

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau(43) International Publication Date  
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number  
WO 2004/033418 A2(51) International Patent Classification<sup>7</sup>: C07C 311/00[CH/CH]; ACTELION Pharmaceuticals Ltd., Obertorweg  
64, CH-4123 Allschwil (CH).(21) International Application Number:  
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(22) International Filing Date: 6 October 2003 (06.10.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,  
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,  
UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PCT/EP02/11409 11 October 2002 (11.10.2002) EP(71) Applicant (*for all designated States except US*):  
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KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Thann, F-F-68116 Guewenheim (FR). FISCHLI, Walter**Published:**— *without international search report and to be republished  
upon receipt of that report**For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*(54) Title: SULFONYLAMINO-ACETIC ACID DERIVATIVES(57) **Abstract:** The invention relates to novel sulfonylamino-acetic acid derivatives and their use as active ingredients in the prepa-  
ration of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of such  
compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor  
antagonists.

WO 2004/033418 A2

ACTELION 26A/OR4

**Sulfonylamino-acetic acid Derivatives**

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The present invention relates to novel sulfonylamino-acetic acid derivatives of the general formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including pharmaceutical compositions containing one or more compounds of formula I, and especially their use as orexin receptor antagonists.

10 The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, *Cell*, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, *Cell*, 1998, 15 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, *Cell*, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals which belong to the G-protein coupled receptor superfamily (Sakurai T. *et al.*, *Cell*, 1998, 92, 573-585), the orexin-1 receptor (OX<sub>1</sub>) 20 which is selective for OX-A and the orexin-2 receptor (OX<sub>2</sub>) which is capable to bind OX-A as well as OX-B.

Orexin receptors are found in the mammalian host and may be responsible for many pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic 25 disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's 30 syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcer; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia);

functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. by HIV; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; delayed or advanced sleep phase syndrome; sleep related dystonias; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders including febrile seizures and other hyperthermia disorders; and other diseases related to orexin.

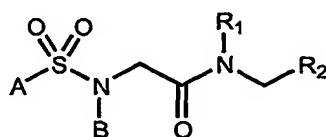
Up to now some low molecular weight compounds are known which have a potential to antagonise either specifically OX<sub>1</sub> or OX<sub>2</sub>, or both receptors at the same time. In WO 99/09024, WO 99/58533, WO 00/47576, WO 00/47577 and WO 00/47580 formerly SmithKline Beecham reported phenylurea, phenylthiourea and cinnamide derivatives as OX<sub>1</sub> selective antagonists. More recently WO 01/85693 from Banyu Pharmaceuticals has been published wherein N-acyltetrahydroisoquinoline derivatives are disclosed. 2-Amino-methylpiperidine derivatives (WO 01/96302), 3-aminomethyl-morpholine derivatives (WO 02/44172) and N-aroyle cyclic amines (WO 02/89800, WO 02/90355, WO 03/51368 and WO 03/51871) have been suggested by formerly SmithKline Beecham as orexin receptor antagonists. Related compounds are disclosed in WO 03/02559, WO 03/02561, WO 03/32991, WO 03/41711, WO 03/51872 and WO 03/51873. In WO 03/37847 formerly SmithKline Beecham reported benzamide

derivatives as orexin receptor antagonists. International patent applications WO 01/68609 and WO 02/51838 disclose 1,2,3,4-tetrahydroisoquinoline and novel benzazepine derivatives as orexin receptor antagonists. The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

The present invention comprises sulfonylamino-acetic acid derivatives which are non-peptide antagonists of the human orexin receptors, in particular the human orexin-2 receptor. These compounds, therefore, are of potential use in the treatment of disturbed homeostasis and eating disorders (e.g. bulimia, obesity, food abuse, compulsive eating or irritable bowel syndrome), as well as disturbed sleep/wake schedule, sleep disorders (e.g. insomnias, apneas, dystonias) or stress-related diseases (e.g. anxiety, mood and blood pressure disorders) or any other disease related to orexin dysfunction.

WO 00/50391 discloses certain sulfonamide derivatives as modulators of the production of amyloid  $\beta$ -protein. WO 02/32864 discloses certain sulfanilide derivatives useful in the treatment of diseases mediated by oxytocin and/or vasopressin.

The present invention relates to novel sulfonylamino-acetic acid derivatives of the general formula (I).



Formula (I)

wherein:

A represents 4-ethylphenyl-, 4-isopropylphenyl-, 4-*tert.*-butylphenyl-, 2-methylphenyl-, 3-methylphenyl-, 4-cyclopropylphenyl-, 3-fluorophenyl-, 2-chlorophenyl-, 3-chlorophenyl-, 4-bromophenyl-, 2-trifluoromethylphenyl-, 3-trifluoromethylphenyl-, 4-(1-hydroxy-1-methyl-ethyl)-phenyl-, 3-chloro-4-methylphenyl-, 2-methoxy-4-methylphenyl-, 3,4-difluorophenyl-, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl, 2-formyl-1,2,3,4-tetrahydroisoquinolin-7-yl, phenylethenyl-, 1-naphthyl-, 2-naphthyl-,



3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 5-isopropyl-pyridin-2-yl, 6-dimethylamino-pyridin-3-yl, 6-bromo-5-chloro-pyridin-3-yl or 8-quinolinyl-;

5 B represents a phenyl, a 6-membered heteroaryl or a nine- or ten-membered bicyclic heteroaryl group, which groups are unsubstituted or independently mono- or di- substituted with cyano, halogen, hydroxy, lower alkyl, hydroxy lower alkyl, amino lower alkyl, aminocarbonyl lower alkyl, sulfonylamino lower alkyl, lower alkenyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl lower alkyloxy, amino, aminocarbonyl or sulfonylamino; or a cyclohexyl, 3-  
10 piperidiny1 or 4-piperidiny1 group, which groups are unsubstituted or mono-substituted with hydroxy, lower alkyl, hydroxy lower alkyl, aminocarbonyl lower alkyl, sulfonylamino lower alkyl, amino, aminocarbonyl or sulfonylamino;  
with the proviso that in case A represents 2-methylphenyl- or 4-bromophenyl the phenyl ring as represented by B is substituted;

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R<sup>1</sup> represents lower alkyl, cycloalkyl, hydroxy lower alkyl or cyano lower alkyl;

R<sup>2</sup> represents lower alkyl, lower alkenyl, hydroxy lower alkyl, amino lower alkyl, sulfonylamino lower alkyl, cycloalkyl; an unsubstituted or mono- or disubstituted phenyl  
20 group substituted independently with cyano, halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino; an unsubstituted or mono- or di-substituted five- or six-membered heteroaryl group substituted independently with cyano, halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino; an unsubstituted or mono- or di-substituted  
25 nine- or ten-membered bicyclic heteroaryl group substituted independently with cyano, halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of  
30 diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

In the present description the term "lower alkyl", alone or in combination, means a straight-chain or branched-chain alkyl group with 1-5 carbon atoms as for example methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, tert.-butyl, isobutyl and the isomeric pentyls.

5 The term "lower alkenyl" means a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, means a group of the formula lower alkyl-O- in which the term "lower alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, preferably methoxy and ethoxy.

10 The term "cycloalkyl", alone or in combination, means a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C<sub>3</sub>-C<sub>6</sub> cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, preferably cyclopropyl, cyclohexyl and particularly cyclohexyl or lower alkyl substituted cycloalkyl which may preferably be substituted with lower alkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl or dimethyl-cyclohexyl.

The term "aryl" means a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, amino, or carboxy.

20 The term "aralkyl" means a lower alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined.

The term "heterocyclyl" means a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or different. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl, dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

The term "6-membered heteroaryl group" means e.g. a pyridyl, pyrimidinyl, pyrazinyl or a pyridazinyl group.

The term "nine- or ten-membered bicyclic heteroaryl group" means e.g. an indazolyl, indolyl, isoindolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, phthalazinyl, cinnolinyl, quinazolinyl or a naphthyridinyl group.

The term "5-membered heteroaryl group" means e.g. a pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thiadiazolyl group.

The term "amino" in terms like "amino", "amino lower alkyl", "aminocarbonyl" or "aminocarbonyl lower alkyl" represents a  $\text{NH}_2$ -,  $\text{NHR}^3$ - or a  $\text{NR}^3\text{R}^4$ -group.  $\text{R}^3$  and  $\text{R}^4$  are lower alkyl groups, which might be equal or different.

The term "sulfonylamino" in terms like "sulfonylamino" or "sulfonylaminoalkyl" represents a  $\text{R}^5\text{S}(\text{O})_2\text{NR}^3$ -group.  $\text{R}^5$  represents a lower alkyl group, a phenyl group, a 6-membered heteroaryl group or a 5-membered heteroaryl group.

The term "halogen" means fluorine, chlorine, bromine or iodine and preferably chlorine and bromine and particularly chlorine.

A preferred group of compounds of formula (I) are those in which B,  $\text{R}^1$  and  $\text{R}^2$  have the meaning given in formula (I) above and A represents a 4-ethylphenyl group; and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B,  $\text{R}^1$  and  $\text{R}^2$  have the meaning given in formula (I) above and A represents a 4-isopropylphenyl group; and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B,  $\text{R}^1$  and  $\text{R}^2$  have the meaning given in formula (I) above and A represents a 4-*tert*.-butylphenyl group;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

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Another preferred group of compounds of formula (I) are those in which B,  $R^1$  and  $R^2$  have the meaning given in formula (I) above and A represents a 2-methylphenyl group;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and  
10 the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B,  $R^1$  and  $R^2$  have the meaning given in formula (I) above and A represents a 3-methylphenyl group;

15 and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

20 Another preferred group of compounds of formula (I) are those in which B,  $R^1$  and  $R^2$  have the meaning given in formula (I) above and A represents a 4-(1-hydroxy-1-methyl-ethyl)-phenyl group;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and  
25 the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B,  $R^1$  and  $R^2$  have the meaning given in formula (I) above and A represents a 3-chloro-4-methylphenyl group;

30 and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in formula (I) above and A represents a 2-formyl-1,2,3,4-tetrahydroisoquinolin-7-yl group;

5 and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

10 Another preferred group of compounds of formula (I) are those in which B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in formula (I) above and A represents a 2-naphthyl group; and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological  
15 forms, thereof.

Another preferred group of compounds of formula (I) are those in which B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in formula (I) above and A represents a 3-methyl-pyridin-2-yl group; and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of  
20 diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

Another preferred group of compounds of formula (I) are those in which B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in formula (I) above and A represents a 5-isopropyl-pyridin-2-yl group; and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological  
25 forms, thereof.

30 Another preferred group of compounds of formula (I) are those in which B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in formula (I) above and A represents a 6-dimethylamino-pyridin-3-yl group;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

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Examples of preferred compounds of formula (I) are:

2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-diethyl-acetamide;

*N,N*-Diethyl-2-[(naphthalene-2-sulfonyl)-p-tolyl-amino]-acetamide;

*N,N*-Diethyl-2-[(toluene-3-sulfonyl)-p-tolyl-amino]-acetamide;

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*N,N*-Diethyl-2-[(4-ethyl-benzenesulfonyl)-p-tolyl-amino]-acetamide;

*N,N*-Diethyl-2-[(toluene-2-sulfonyl)-p-tolyl-amino]-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-phenyl-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(4-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-cyclohexyl-amino]-*N,N*-diethyl-acetamide;

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2-[(4-tert-Butyl-benzenesulfonyl)-(4-methyl-cyclohexyl)-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(6-chloro-pyridin-3-yl)-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(3-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-m-tolyl-amino]-*N,N*-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-o-tolyl-amino]-*N,N*-diethyl-acetamide;

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2-[(4-tert-Butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-cyclopropyl-methyl-*N*-n-propyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(6-chloro-pyridin-3-yl)-amino]-*N*-cyclo-propylmethyl-*N*-n-propyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-m-tolyl-amino]-*N*-cyclopropylmethyl-*N*-n-propyl-  
25 acetamide;

2-[(6-Dimethylamino-pyridine-3-sulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-di-n-propyl-acetamide;

*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-acetamide;

30 

2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-4-ylmethyl-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(toluene-2-sulfonyl)-p-tolyl-amino]-acetamide;

*N,N*-Diethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

- 2-[(4-tert-Butyl-benzenesulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N,N*-diethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;
- N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;
- 5 *N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;
- N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-ethyl-acetamide;
- N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(naphthalene-2-sulfonyl)-amino]-acetamide;
- 10 *N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(naphthalene-2-sulfonyl)-amino]-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide;
- N,N*-Diethyl-2-[(4-isopropyl-benzenesulfonyl)-*p*-tolyl-amino]-acetamide;
- 2-[(3-Chloro-4-methyl-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide;
- N,N*-Diethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetamide;
- 15 *N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-hydroxy-ethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-bis-(2-hydroxy-ethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-cyano-ethyl)-*N*-ethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-
- 20 acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 25 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide;
- N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-(2-hydroxy-ethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-
- 30 acetamide;
- N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N,N*-diethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;
- 5 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 10 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(4-dimethylamino-benzyl)-*N*-ethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-(3-hydroxy-benzyl)-acetamide;
- 15 2-[(4-tert-Butyl-benzenesulfonyl)-[(ethyl-thiazol-2-ylmethyl-carbamoyl)-methyl]-amino]-benzamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-{[ethyl-(6-methyl-pyridin-2-ylmethyl)-carbamoyl]-methyl}-amino]-benzamide;
- 2-[(Benzyl-ethyl-carbamoyl)-methyl]-(4-tert-butyl-benzenesulfonyl)-amino]-benzamide;
- 20 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N,N*-diethyl-acetamide;
- N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-(2-hydroxy-ethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide;
- 25 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;
- 30 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-acetamide;



- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(3-hydroxy-propyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 5 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-(3-hydroxy-propyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 10 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(6-dimethylamino-pyridin-2-ylmethyl)-*N*-ethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3,4-dimethoxy-benzyl)-acetamide;
- 15 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3-methyl-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3,5-dimethoxy-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-methyl-*N*-pyridin-3-ylmethyl-
- 20 acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 25 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-cyclopropyl-*N*-(3-methyl-benzyl)-acetamide;
- N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide;
- N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-*N*-(6-methyl-pyridin-2-
- 30 ylmethyl)-acetamide;
- N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide;

*N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

5 *N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide;

*N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

10 *N*-(2-Cyano-ethyl)-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-(1-methyl-1H-pyrrol-2-ylmethyl)-acetamide;

*N*-Ethyl-*N*-(4-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

15 *N*-Ethyl-*N*-(3-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide;

20 *N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide;

25 *N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-(2-Cyano-ethyl)-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;

30 *N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(1-methyl-1H-pyrrol-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(toluene-2-sulfonyl)-p-tolyl-amino]-acetamide;

*N*-Ethyl-*N*-pyridin-3-ylmethyl-2-[(toluene-2-sulfonyl)-p-tolyl-amino]-acetamide;

*N*-Ethyl-*N*-thiazol-2-ylmethyl-2-[(toluene-2-sulfonyl)-p-tolyl-amino]-acetamide;

*N*-Ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide;

*N*-(2-Hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide;

5 *N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

10 *N*-Ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-*N*-pyridin-2-ylmethyl-2-[(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetamide;

15 *N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

20 *N*-Benzyl-*N*-ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetamide;

*N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

25 *N*-Benzyl-*N*-ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetamide;

2-[(4-*tert*-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;

30 *N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

- 5 2-[(3-Dimethylamino-phenyl)-[4-(1-hydroxy-1-methyl-ethyl)-benzenesulfonyl]-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;

Examples of particularly preferred compounds of formula (I) are:

- 10 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-diethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-(4-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-(3-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-m-tolyl-amino]-*N,N*-diethyl-acetamide;  
 2-[(6-Dimethylamino-pyridine-3-sulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-  
 15 acetamide;  
*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-4-ylmethyl-  
 acetamide;  
*N,N*-Diethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;  
 20 *N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;  
*N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;  
*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-ethyl-  
 acetamide;  
*N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(naphthalene-2-sulfonyl)-amino]-  
 25 acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide;  
 2-[(3-Chloro-4-methyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-diethyl-acetamide;  
*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(2-hydroxy-ethyl)-  
 acetamide;  
 30 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(2-cyano-ethyl)-*N*-ethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-  
 acetamide;

- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 5 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N,N*-diethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;
- 10 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-(3-hydroxy-benzyl)-acetamide;
- 15 2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 20 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 25 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide;
- N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;
- 30 *N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Ethyl-*N*-(3-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

5 *N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide;

10 *N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

15 2-[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;

*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-acetamide;

20 *N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

The present invention encompasses physiologically usable or pharmaceutically acceptable salts of compounds of formula (I). This encompasses salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as formic acid, methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid and the like. The compounds of formula (I) which are acidic can also form salts with physiologically compatible bases.

Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

The present invention encompasses also solvation complexes of compounds of general formula (I). The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of general formula (I).

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of general formula (I) and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of formula (I) might have one or several asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates and the meso-forms.

Preferred compounds as described above have  $IC_{50}$  values below 100 nM, particularly preferred compounds have  $IC_{50}$  values below 20 nM which have been determined with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

The compounds of formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity, diabetes, prolactinoma, narcolepsy, insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia and dementia or any other disease related to orexin dysfunction.

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of disturbed homeostasis and eating disorders (e.g. bulimia, obesity, food abuse, compulsive eating or irritable bowel syndrome), as well as disturbed sleep/wake schedule, sleep disorders (e.g. insomnias, apneas, dystonias), stress-related diseases (e.g. anxiety, mood and blood pressure disorders), or any other disease related to orexin dysfunction.

The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered enterally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions), or topically, e.g. in the form of ointments, creams or oils.

The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules. Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc. Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc. Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc. Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. The compounds of formula (I) may also be used in combination with one or more other therapeutically useful substances. Examples are anorectic drugs like fenfluramine and related substances; lipase inhibitors like orlistat and related substances; antidepressants like fluoxetine and related substances; anxiolytics like alprazolam and related substances; sleep-inducers like zopiclone and related substances; or any other therapeutically useful substance.

The dosage of compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the



mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to 1000 mg, especially about 50 mg to about 500 mg, comes into consideration.

5           The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula (I).

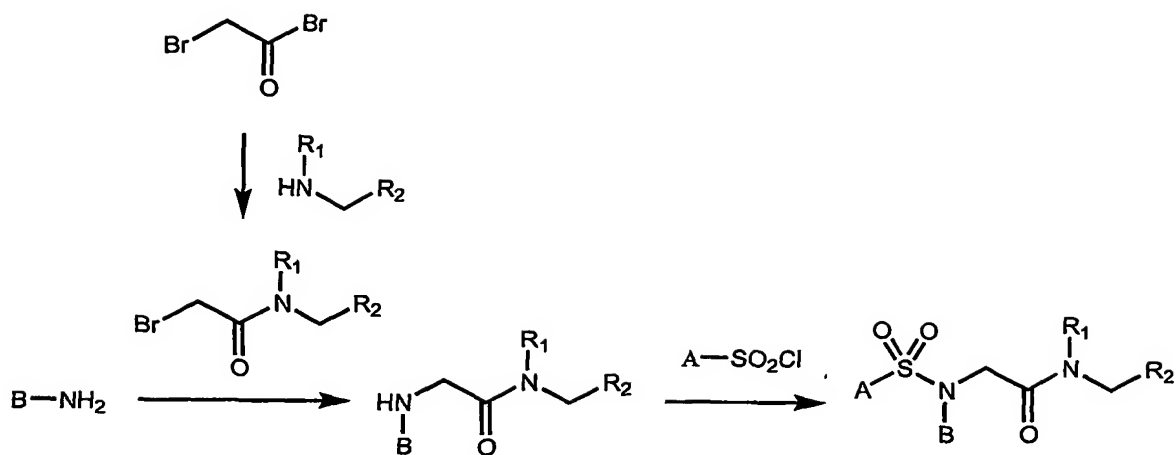
10           The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein A, B, R<sup>1</sup>, R<sup>2</sup> are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atom may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

15           The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

          The compounds of formula (I) may be prepared as single compounds or as libraries of compounds comprising at least 2, typically 5 to 200 compounds of formula (I).

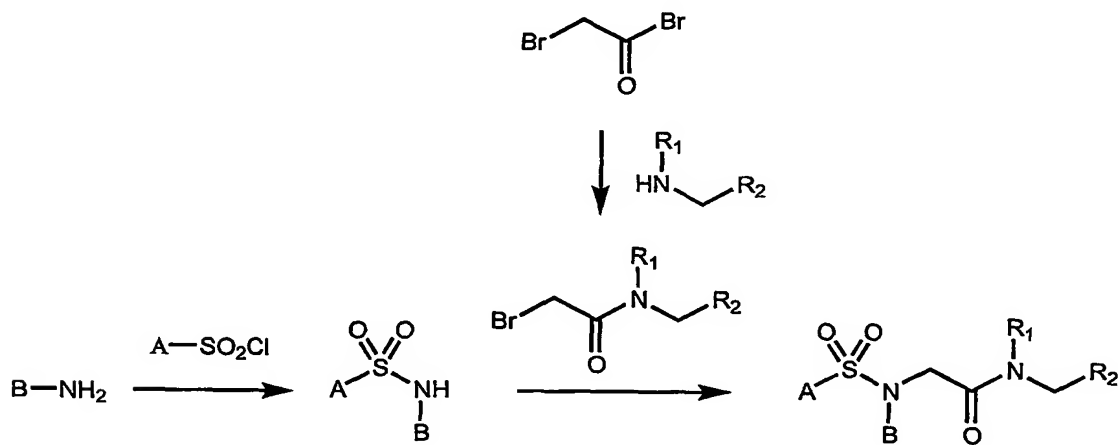
20           Compound libraries are prepared by multiple parallel synthesis using solution phase chemistry.

25           The compounds of formula (I) have been prepared by following one out of three possible synthetic pathways. The first pathway starts with the reaction of an amine B-NH<sub>2</sub> with an  $\alpha$ -bromoacetamide, which might be synthesised starting from bromoacetyl bromide and an amine NHR<sup>1</sup>(CH<sub>2</sub>R<sup>2</sup>) either *in situ* or separately. In a second step the respective aminoacetamide was reacted with a sulfonyl chloride A-SO<sub>2</sub>Cl (*Scheme 1*).



Scheme 1

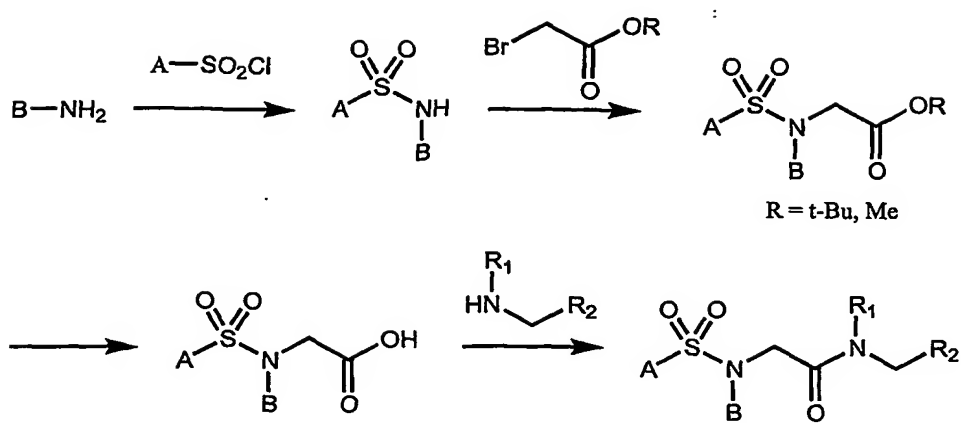
The second synthetic route starts with the reaction of an amine B-NH<sub>2</sub> with a  
 5 sulfonyl chloride A-SO<sub>2</sub>Cl. From the intermediate sulfonamides the target molecules can be  
 obtained by reaction with the respective  $\alpha$ -bromoacetamide (Scheme 2).



Scheme 2

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In a third pathway a sulfonamide is synthesized starting from an amine B-NH<sub>2</sub> and a  
 sulfonyl chloride A-SO<sub>2</sub>Cl. The obtained sulfonamide is transformed to a t-butyl- or methyl  
 acetate derivative by reaction with either tert-butyl bromoacetate or methyl bromoacetate.  
 15 The ester is hydrolyzed and the obtained acid is coupled with an amine NHR<sup>1</sup>(CH<sub>2</sub>R<sup>2</sup>) to  
 give the desired amide (Scheme 3).



Scheme 3

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## Experimental Section

### Abbreviations:

	bp	Boiling point
5	BSA	Bovine serum albumine
	CHO	Chinese hamster ovary
	d	Day(s)
	DCM	Dichloromethane
	DMSO	Dimethylsulfoxide
10	DIPEA	<i>N,N</i> -Diisopropylethylamine
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
	ES	Electron spray
	ether	Diethylether
	FCS	Foetal calf serum
15	FLIPR	Fluorescent imaging plate reader
	h	Hour(s)
	HBSS	Hank's balanced salt solution
	HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
	HPLC	High pressure/performance liquid chromatography
20	MS	Mass spectroscopy
	LC	Liquid chromatography
	min	Minute(s)
	R <sub>t</sub>	retention time
	RT	Room temperature
25	TBTU	<i>O</i> -Benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran

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## **I. Biology**

### **Determination of Orexin receptor antagonistic activity**

5           The Orexin receptor antagonistic activity of the compounds of formula (I) was determined in accordance with the following experimental method.

#### **Experimental method:**

##### **10   Intracellular calcium measurements**

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor and the human orexin-2 receptor, respectively, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and  
15   10 % inactivated foetal calf serum (FCS).

The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO<sub>2</sub>.

20   Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol:water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2  
25   mM HEPES.

On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

30   The 96-well plates were incubated for 60 min at 37° C in 5% CO<sub>2</sub>. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well.

Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of  
35   agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak

induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist,  $IC_{50}$  value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined. Selected compounds are displayed in *Table 1*.

5

	OX <sub>1</sub> : $IC_{50}$ [nM]	OX <sub>2</sub> : $IC_{50}$ [nM]
Example 46	898	5
Example 47	354	4
Example 63	>10000	3
Example 66	1026	4
Example 71	417	5
Example 87	56	8
Example 111	331	5
Example 158	840	5
Example 160	8636	2
Example 162	>10000	2
Example 163	>10000	4
Example 185	4269	4
Example 207	5368	4

*Table 1*

## **II. Chemistry**

10

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof.

All temperatures are stated in °C.

All analytical and preparative HPLC investigations were performed using RP-C18 based columns.

15

### **A Synthesis of starting materials**

#### **A.1 Synthesis of amines**

##### **A1.1 Synthesis of amines via reductive amination (general procedure):**

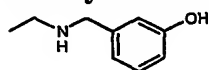
20

A solution of the respective amine in THF (2.0 mol/L, 5.0 mL) was added to a solution of the respective aldehyde (10.0 mmol) in methanol (20 mL). Activated molecular sieves (4Å) were added and the reaction mixture was stirred for 16 h. After addition of sodium borohydride (12 mmol) the solution was stirred for 3 h, treated with water (10 mL), stirred for 1 h and purified by ion-exchange chromatography [amberlyst 15, methanol / ammonium hydroxide solution (10 mol/L) 1:1]. After removal of methanol in vacuo the aqueous layer was extracted with ethyl

25

acetate (3 x 100 mL). The solvents were removed in vacuo, the residue was dissolved in ethanol and the product was precipitated by addition of a solution of hydrogen chloride in ether (2.0 mol/L). The following amines were obtained:

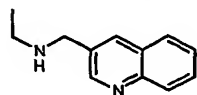
5 **3-Ethylaminomethyl-phenol:**



prepared by reaction of ethylamine with 3-hydroxy-benzaldehyde

LC-MS:  $rt = 0.55$  min, 152 ( $M+1$ ,  $ES^+$ ).

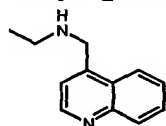
10 **Ethyl-quinolin-3-ylmethyl-amine:**



prepared by reaction of ethylamine with quinoline-3-carbaldehyde

LC-MS:  $rt = 0.58$  min, 187 ( $M+1$ ,  $ES^+$ ).

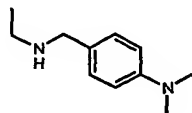
15 **Ethyl-quinolin-4-ylmethyl-amine:**



prepared by reaction of ethylamine with quinoline-4-carbaldehyde

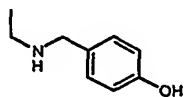
LC-MS:  $rt = 0.50$  min, 187 ( $M+1$ ,  $ES^+$ ).

20 **(4-Ethylaminomethyl-phenyl)-dimethyl-amine:**



prepared by reaction of ethylamine with 4-dimethylamino-benzaldehyde

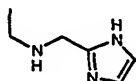
LC-MS:  $rt = 0.49$  min, 179 ( $M+1$ ,  $ES^+$ ).

**4-Ethylaminomethyl-phenol:**

prepared by reaction of ethylamine with 4-hydroxy-benzaldehyde

LC-MS:  $rt = 0.54$  min, 152 (M+1, ES+).

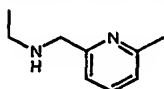
5

**Ethyl-(1H-imidazol-2-ylmethyl)-amine:**

prepared by reaction of ethylamine with 1H-imidazole-2-carbaldehyde

LC-MS:  $rt = 0.16$  min, 126 (M+1, ES+).

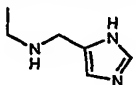
10

**Ethyl-(6-methyl-pyridin-2-ylmethyl)-amine:**

prepared by reaction of ethylamine with 6-methyl-pyridine-2-carbaldehyde

LC-MS:  $rt = 0.48$  min, 151 (M+1, ES+).

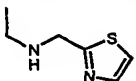
15

**Ethyl-(3H-imidazol-4-ylmethyl)-amine:**

prepared by reaction of ethylamine with 3H-imidazole-4-carbaldehyde

LC-MS:  $rt = 0.16$  min, 126 (M+1, ES+).

20

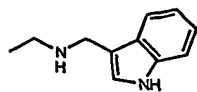
**Ethyl-thiazol-2-ylmethyl-amine:**

prepared by reaction of ethylamine with thiazole-2-carbaldehyde

LC-MS:  $rt = 0.17$  min, 143 (M+1, ES+).

25

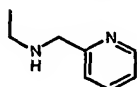


**Ethyl-(1H-indol-3-ylmethyl)-amine:**

prepared by reaction of ethylamine with 1H-indole-3-carbaldehyde

LC-MS:  $rt = 0.75$  min, 175 ( $M+1$ , ES+).

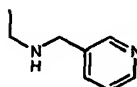
5

**Ethyl-pyridin-2-ylmethyl)-amine:**

prepared by reaction of ethylamine with pyridine-2-carbaldehyde

LC-MS:  $rt = 0.47$  min, 137 ( $M+1$ , ES+).

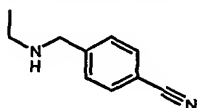
10

**Ethyl-pyridin-3-ylmethyl)-amine:**

prepared by reaction of ethylamine with pyridine-3-carbaldehyde

LC-MS:  $rt = 0.16$  min, 137 ( $M+1$ , ES+).

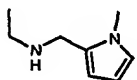
15

**4-Ethylaminomethyl-benzonitrile:**

prepared by reaction of ethylamine with 4-formyl-benzonitrile

LC-MS:  $rt = 0.62$  min, 161 ( $M+1$ , ES+).

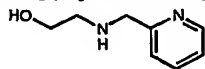
20

**Ethyl-(1-methyl-1H-pyrrol-2-ylmethyl)-amine:**

prepared by reaction of ethylamine with 1-methyl-1H-pyrrole-2-carbaldehyde

LC-MS:  $rt = 0.56$  min, 139 ( $M+1$ , ES+).

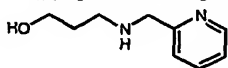
25

**2-[(Pyridin-2-ylmethyl)-amino]-ethanol:**

prepared by reaction of 2-amino-ethanol with pyridine-2-carbaldehyde

LC-MS:  $rt = 0.16$  min, 153 ( $M+1$ ,  $ES^+$ ).

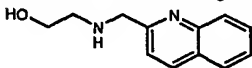
5

**3-[(Pyridin-2-ylmethyl)-amino]-propan-1-ol:**

prepared by reaction of 3-amino-propan-1-ol with pyridine-2-carbaldehyde

LC-MS:  $rt = 0.16$  min, 167 ( $M+1$ ,  $ES^+$ ).

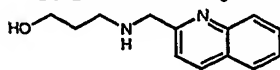
10

**2-[(Quinolin-2-ylmethyl)-amino]-ethanol:**

prepared by reaction of 2-amino-ethanol with quinoline-2-carbaldehyde

LC-MS:  $rt = 0.53$  min, 203 ( $M+1$ ,  $ES^+$ ).

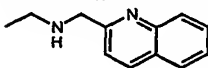
15

**3-[(Quinolin-2-ylmethyl)-amino]-propan-1-ol:**

prepared by reaction of 3-amino-propan-1-ol with quinoline-2-carbaldehyde

LC-MS:  $rt = 0.56$  min, 217 ( $M+1$ ,  $ES^+$ ).

20

**Ethyl-quinolin-2-ylmethyl-amine:**

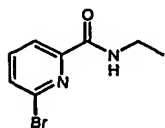
prepared by reaction of ethylamine with quinoline-2-carbaldehyde

LC-MS:  $rt = 0.58$  min, 187 ( $M+1$ ,  $ES^+$ ).

25

## A1.2 Synthesis of 6-Ethylaminomethyl-pyridin-2-ylamines:

### A1.2.1 Synthesis of 6-Bromo-pyridine-2-carboxylic acid ethylamide:

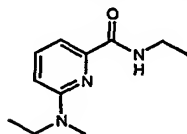


TBTU (6.5 mmol) was added to a solution of 6-bromo-pyridine-2-carboxylic acid (5.0 mmol) in DMF (30 mL). A solution of ethylamine in THF (1.0 mol/L, 5.0 mL) and DIPEA (15.0 mmol) were added and the reaction mixture was stirred for 16 h. Water (100 mL) and ethyl acetate (100 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give 1.1 g (4.8 mmol, 96%) of the desired amide as a yellow oil which was used without further purification. LC-MS: rt = 0.85 min, 229 (M+1, ES+).

### A1.2.2 Synthesis of 6-Amino-pyridine-2-carboxylic acid ethylamides (general procedure):

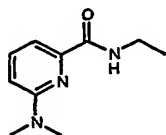
A solution of the respective amine in methanol (2.0 mol/L, 5.0 mL) was added to 6-bromo-pyridine-2-carboxylic acid ethylamide (4.38 mmol). The reaction mixture was heated for 5 min in a microwave oven at 150W and purified by preparative HPLC chromatography to give the following aminopyridines:

#### 6-(Ethyl-methyl-amino)-pyridine-2-carboxylic acid ethylamide:



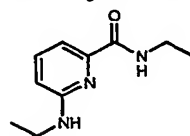
prepared by reaction of ethyl-methyl-amine with 6-bromo-pyridine-2-carboxylic acid ethylamide

LC-MS: rt = 0.82 min, 208 (M+1, ES+).

**6-Dimethylamino-pyridine-2-carboxylic acid ethylamide:**

prepared by reaction of dimethyl-amine with 6-bromo-pyridine-2-carboxylic acid ethylamide

5 LC-MS:  $rt = 0.72$  min, 194 (M+1, ES+).

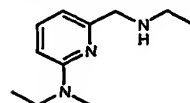
**6-Ethylamino-pyridine-2-carboxylic acid ethylamide:**

prepared by reaction of ethylamine with 6-bromo-pyridine-2-carboxylic acid ethylamide; in contrast to the general procedure the reaction was carried out by heating a solution of the starting materials in ethanol/water for 72 h at 100°C in an autoclave

LC-MS:  $rt = 0.55$  min, 194 (M+1, ES+).

15 **A1.2.3 Synthesis of 6-Ethylaminomethyl-pyridin-2-ylamines (general procedure):**

Lithium aluminum hydride (7.6 mmol) was added to a solution of the respective 6-amino-pyridine-2-carboxylic acid ethylamide (3.8 mmol) in THF (10 mL). The reaction mixture was stirred for 2 h at RT and for 7 h at reflux, allowed to reach RT, treated with water (0.50 mL), NaOH solution (2.0 mol/L, 0.50 mL) and water (1.50 mL) and filtered. The residue was washed with ethyl acetate (3 x 20 mL) and the filtrate was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give the following pyridine derivatives:

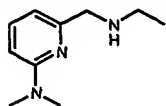
**Ethyl-(6-ethylaminomethyl-pyridin-2-yl)-methyl-amine:**

prepared by reduction of 6-(ethyl-methyl-amino)-pyridine-2-carboxylic acid ethylamide

25

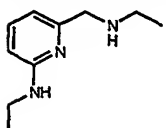
LC-MS:  $rt = 0.50$  min, 194 (M+1, ES+).

**(6-Ethylaminomethyl-pyridin-2-yl)-dimethyl-amine:**



- 5 prepared by reduction of 6-dimethylamino-pyridine-2-carboxylic acid ethylamide  
LC-MS:  $rt = 0.42$  min, 180 (M+1, ES+).

**Ethyl-(6-ethylaminomethyl-pyridin-2-yl)-amine:**

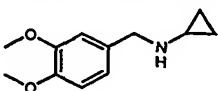


- 10 prepared by reduction of 6-ethylamino-pyridine-2-carboxylic acid ethylamide  
LC-MS:  $rt = 0.46$  min, 180 (M+1, ES+).

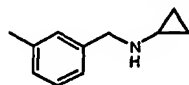
**A1.3 Synthesis of Benzyl-cyclopropyl-amines (general procedure):**

- 15 Cyclopropylamine (30.0 mmol) was added to a solution of the respective  
benzaldehyde (30.0 mmol) in methanol (30 mL). After 2 h sodium borohydride  
(30.0 mmol) was added. The reaction mixture was stirred for 2 h, treated with an  
aqueous NaOH-solution (1.0 mol/L, 2.0 mL), and concentrated in vacuo. Ethyl  
acetate (100 mL) and an aqueous NaOH-solution (1.0 mol/L, 50 mL) were added,  
and the layers were separated. The organic layer was washed with an aqueous  
20 NaOH-solution (1.0 mol/L, 30 mL) and brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and  
concentrated in vacuo to give the following amines which were used without  
further purification:

**Cyclopropyl-(3,4-dimethoxy-benzyl)-amine:**

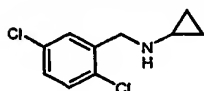


- 25 prepared by reaction of cyclopropylamine with 3,4-dimethoxy-benzaldehyde  
LC-MS:  $rt = 0.67$  min, 208 (M+1, ES+).

**Cyclopropyl-(3-methyl-benzyl)-amine:**

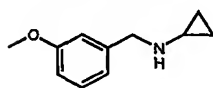
prepared by reaction of cyclopropylamine with 3-methyl-benzaldehyde

5 LC-MS:  $rt = 0.53$  min, 162 ( $M+1$ ,  $ES^+$ ).

**Cyclopropyl-(2,5-dichloro-benzyl)-amine:**

prepared by reaction of cyclopropylamine with 2,5-dichloro-benzaldehyde.

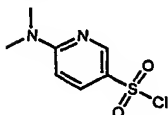
10

**Cyclopropyl-(3-methoxy-benzyl)-amine:**

prepared by reaction of cyclopropylamine with 3-methoxy-benzaldehyde

LC-MS:  $rt = 0.52$  min, 178 ( $M+1$ ,  $ES^+$ ).

15

**A.2 Synthesis of sulfonyl chlorides****A.2.1 Synthesis of 6-Dimethylamino-pyridine-3-sulfonyl chloride**

20 (5-Bromo-pyridin-2-yl)-dimethyl-amine:

*N*-Bromosuccinimide (190 mmol) was added portionwise to a solution of 2-(dimethylamino)-pyridine (200 mmol) in DCM (1.0 L). After 10 min a HPLC-MS indicated complete conversion. The solvent was removed in vacuo and the residue was purified by flash-chromatography (ethyl acetate/heptane 1:19) to give

25 25.7 g (128 mmol, 64%) of the desired arylbromide as a white solid.

LC-MS:  $rt = 0.46$  min, 201 ( $M+1$ ,  $ES^+$ ).

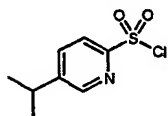
**6-Dimethylamino-pyridine-3-thiol:**

At -78°C a solution of (5-bromo-pyridin-2-yl)-dimethyl-amine (15.0 mmol) in THF (50 mL) was added dropwise to a solution of *n*-BuLi in Hexane (1.6 mol/L, 10.0 mL). The reaction mixture was stirred for 15 min and sulfur (20.0 mmol) was added. After 1 min a solution of *n*-BuLi in Hexane (1.6 mol/L, 20.0 ml) was added. The reaction mixture was stirred for 10 min at -78°C and purified immediately by flash-chromatography (ethyl acetate/heptane 1:3) without previous work-up. A second flash-chromatography (gradient: ethyl acetate/heptane 1:19 to 1:9) yielded 0.50 g (3.24 mmol, 21%) of 6-dimethylamino-pyridine-3-thiol as a yellow oil.

LC-MS: *rt* = 0.46 min, 155 (*M*+1, ES+).

**6-Dimethylamino-pyridine-3-sulfonyl chloride:**

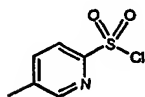
Hydrochloric acid (25%, 1.13 mL) was added to a solution of 6-dimethylamino-pyridine-3-thiol (0.50 mmol) in DCM (10 mL) at -78°C. A solution of sodium hypochlorite in water (6-14%, 5.2 mL) was added at -78°C and the reaction mixture was stirred for additional 2 min. The layers were separated and the aqueous layer was extracted with DCM (3 x 20 mL). The solvents were removed in vacuo and the obtained 6-dimethylamino-pyridine-3-sulfonyl chloride was used immediately in the next synthetic step.

**A.2.2 Synthesis of 5-Isopropyl-pyridine-2-sulfonyl chloride**

Hydrochloric acid (25%, 63 mL) was added to a suspension of 5-isopropyl-pyridine-2-thiol (90 mmol) in DCM (150 mL) at RT. The reaction mixture was cooled to -15°C, a solution of sodium hypochlorite in water (6-14%, 240 mL) was added dropwise and the reaction mixture was stirred for additional 15 min. After separation of the layers DCM (150 mL) was added to the aqueous layer. Another portion of a solution of sodium hypochlorite in water (6-14%, 90 mL) was added at -15°C. The layers were separated and the aqueous layer was extracted with

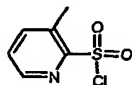
DCM (2 x 150 mL). All organic layers were combined and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvents were removed in vacuo and the obtained 5-isopropyl-pyridine-2-sulfonyl chloride was used immediately in the next synthetic step.

### 5 A.2.3 Synthesis of 5-Methyl-pyridine-2-sulfonyl chloride



Hydrochloric acid (25%, 21 mL) was added to a suspension of 5-methyl-pyridine-2-thiol (30 mmol) in DCM (50 mL) at RT. The reaction mixture was cooled to -15°C, a solution of sodium hypochlorite in water (6-14%, 80 mL) was added dropwise and the reaction mixture was stirred for additional 15 min. After separation of the layers DCM (150 mL) was added to the aqueous layer. Another portion of a solution of sodium hypochlorite in water (6-14%, 30 mL) was added at -15°C. The layers were separated and the aqueous layer was extracted with DCM (3 x 100 mL). All organic layers were combined and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvents were removed in vacuo and the obtained 5-methyl-pyridine-2-sulfonyl chloride was used immediately in the next synthetic step.

### A.2.4 Synthesis of 3-Methyl-pyridine-2-sulfonyl chloride



20 3-Methyl-pyridine-2-thiol:

Thiourea (174 mmol) was added to a solution of 2-bromo-3-methylpyridine (87 mmol) in ethanol (500 mL). The reaction mixture was refluxed for 5 h, cooled to RT, treated with an aqueous solution of sodium hydroxide (25%, 1.0 mL) and refluxed for additional 60 min. The mixture was concentrated in vacuo to 50 mL, water (300 mL) and ethyl acetate (300 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). Brine (50 mL) was added to the combined organic layers, the layers were separated and the solvents were removed in vacuo. The crude oil was crystallized from ether to give 7.1 g (56.7 mmol, 65%) of the thiol as pale yellow crystals.

30 LC-MS: *rt* = 0.48 min, 126 (*M*+1, ES+).

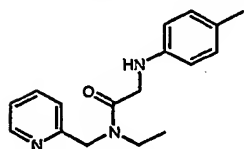


### 3-Methyl-pyridine-2-sulfonyl chloride:

Hydrochloric acid (25%, 9.0 mL) was added to a solution of 3-methyl-pyridine-2-thiol (16 mmol) in DCM (60 mL) at RT. The reaction mixture was cooled to -15°C, a solution of sodium hypochlorite in water (6-14%, 42 mL) was added dropwise and the reaction mixture was stirred for additional 10 min. After separation of the layers the aqueous layer was extracted with DCM (3 x 50 mL). The organic layers were combined and dried with Na<sub>2</sub>SO<sub>4</sub>. The solution of the obtained 3-methyl-pyridine-2-sulfonyl chloride was used immediately in the next synthetic step.

## A.3 Synthesis of other intermediates

### A.3.1 Synthesis of *N*-Ethyl-*N*-pyridin-2-ylmethyl-2-*p*-tolylamino-acetamide



#### *p*-Tolylamino-acetic acid tert-butyl ester:

A solution of *p*-toluidine (200 mmol) in THF (500 mL) was treated with tert-butyl bromoacetate (220 mmol) and DIPEA (440 mmol) at RT. The reaction mixture was heated to reflux for 16 h and cooled to RT. Water (200 mL) and EE (500 mL) were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate (100 mL). The combined organic layers were washed with water and brine. The solvents were removed in vacuo and the residue (44 g) was used without further purification.

LC-MS: *rt* = 0.96 min, 222 (*M*+1, ES+).

#### *p*-Tolylamino-acetic acid:

A solution of crude *p*-tolylamino-acetic acid tert-butyl ester (200 mmol) in DCM (600 mL) was cooled to 0°C and treated with TFA (150 mL). The reaction mixture was allowed to reach RT and stirred for 4 d. Water (200 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (4 x 200 mL). The aqueous layer was adjusted to pH 8 by addition of saturated NaHCO<sub>3</sub> solution and extracted with ethyl acetate (4 x 200 mL). The combined organic layers were dried

with Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed in vacuo to give the crude acid (18 g) which was used in the next step without further purification.

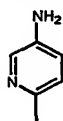
LC-MS: rt = 0.54 min, 166 (M+1, ES+).

5 *N*-Ethyl-*N*-pyridin-2-ylmethyl-2-*p*-tolylamino-acetamide:

A suspension of ethyl-pyridin-2-ylmethyl-amine (29.0 mmol) and DIPEA (78.0 mmol) in DMF (50 mL) was cooled to -20°C and added to a cold (-20°C) solution of *p*-tolylamino-acetic acid (26.0 mmol) and TBTU (34.0 mmol) in DMF (100 mL). The reaction mixture was stirred for 15 min at -20°C. Water (300 mL) and ethyl acetate (400 mL) were added, the layers were separated and the organic layer was washed with water (4 x 100 mL). The combined aqueous layers were extracted with ethyl acetate (200 mL). The combined organic layers were washed with NaOH solution (1.0 mol/L, 100 mL) and brine (100 mL) and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvents were removed in vacuo and the obtained solid was dissolved in ethanol. By addition of a solution of hydrogen chloride in ether a byproduct precipitated which was filtered off. Dilution of the remaining solution with ether led to precipitation of the desired acetamide, which was obtained as a white solid (5.3 g).

LC-MS: rt = 0.64 min, 284 (M+1, ES+).

20 **A.3.2 Synthesis of 6-Methyl-pyridin-3-ylamine**



(6-Methyl-pyridin-3-yl)-carbamic acid benzyl ester:

To a suspension of 6-methylnicotinic acid (36.4 mmol) in toluene (100 mL) was added DIPEA (120 mmol) and Diphenylphosphoryl azide (91.1 mmol). The reaction mixture was heated to reflux for 1 h, cooled to RT and treated with benzyl alcohol (120 mmol). After 30 min ethyl acetate (200 mL) and water (200 mL) were added, the layers were separated and the organic layer was washed with water (3x100 mL). The solvents were removed in vacuo and the residue was purified by preparative HPLC chromatography to give (6-methyl-pyridin-3-yl)-carbamic acid benzyl ester (5.2 g, 21.5 mmol, 59%) as a colourless oil.

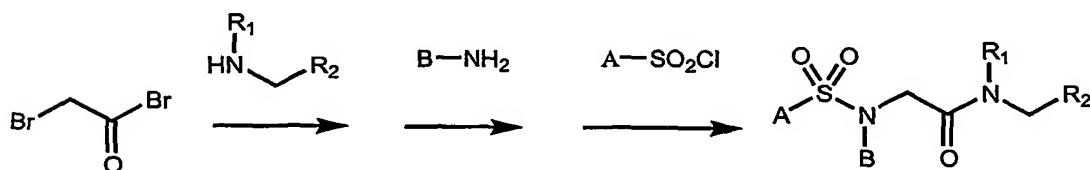
LC-MS:  $rt = 0.68$  min, 243 (M+1, ES+).

#### 6-Methyl-pyridin-3-ylamine:

To a solution of (6-methyl-pyridin-3-yl)-carbamic acid benzyl ester (21.5 mmol) in methanol (100 mL) was added ammonium formate (107 mmol) and palladium on activated carbon (10%, wet, 1.0 g). The reaction mixture was stirred under nitrogen for 1 h and filtered over Celite. The solvents were removed in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with water (2x100 mL) and the combined aqueous layers were extracted with ethyl acetate (3 x 100 mL). The organic layers were combined and dried with  $\text{Na}_2\text{SO}_4$ . The solvents were removed in vacuo and the crude 6-methyl-pyridin-3-ylamine (0.80 g, 7.40 mmol, 34%) was used without further purification.

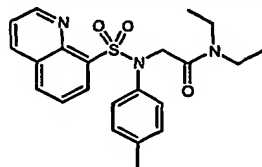
LC-MS:  $rt = 0.16$  min, 109 (M+1, ES+).

### B Synthesis of sulfonylamino-acetic acid derivatives via $\alpha$ -aminoacetamide intermediates (one-pot procedure)



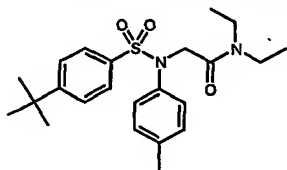
#### General Procedure:

A solution of 2-bromoacetyl bromide (0.30 mmol) in THF (0.50 mL) was cooled to  $0^\circ\text{C}$  and treated dropwise with the respective dialkylamine (0.30 mmol). After addition of ethyldiisopropylamine (1.80 mmol) the reaction mixture was allowed to reach RT and was stirred for 60 min. A solution of the primary amine  $\text{B-NH}_2$  (0.30 mmol) in THF (0.50 mL) was added. The suspension was stirred at  $60^\circ\text{C}$  for 16 h, cooled to RT and treated with a solution of the respective sulfonyl chloride (0.30 mmol) in THF (0.50 mL). After 60 min the solvent was removed in vacuo and the residue was purified by preparative HPLC chromatography to give the following sulfonamides:

**Example 1:*****N,N*-Diethyl-2-[(quinoline-8-sulfonyl)-*p*-tolyl-amino]-acetamide:**

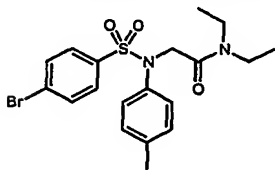
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
8-quinolinesulfonyl chloride

LC-MS: *rt* = 0.92 min, 412 (*M*+1, ES+).

**Example 2:****2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide:**

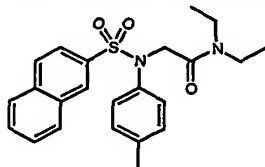
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
4-*tert*-butyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.10 min, 417 (*M*+1, ES+).

**Example 3:****2-[(4-Bromo-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide:**

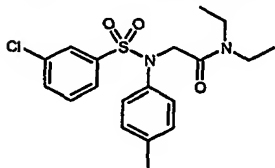
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
4-bromo-benzenesulfonyl chloride

LC-MS: *rt* = 1.04 min, 439 (*M*+1, ES+).

**Example 4:*****N,N*-Diethyl-2-[(naphthalene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

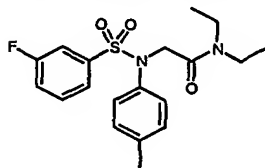
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
 2-naphthalenesulfonyl chloride

LC-MS: *rt* = 1.04 min, 411 (*M*+1, ES+).

**Example 5:****2-[(3-Chloro-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide:**

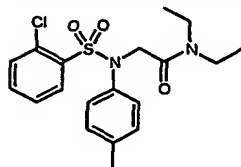
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
 3-chloro-benzenesulfonyl chloride

LC-MS: *rt* = 1.02 min, 395 (*M*+1, ES+).

**Example 6:*****N,N*-Diethyl-2-[(3-fluoro-benzenesulfonyl)-*p*-tolyl-amino]-acetamide:**

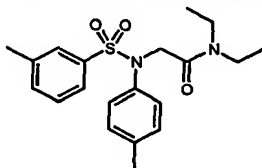
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
 3-fluoro-benzenesulfonyl chloride

LC-MS: *rt* = 0.97 min, 379 (*M*+1, ES+).

**Example 7:****2-[(2-Chloro-benzenesulfonyl)-p-tolyl-amino]-N,N-diethyl-acetamide:**

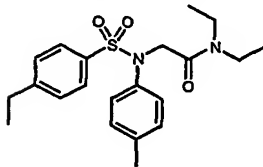
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
2-chloro-benzenesulfonyl chloride

LC-MS: *rt* = 0.98 min, 395 (*M*+1, ES+).

**Example 8:****N,N-Diethyl-2-[(toluene-3-sulfonyl)-p-tolyl-amino]-acetamide:**

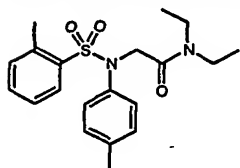
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
toluene-3-sulfonyl chloride

LC-MS: *rt* = 0.99 min, 375 (*M*+1, ES+).

**Example 9:****N,N-Diethyl-2-[(4-ethyl-benzenesulfonyl)-p-tolyl-amino]-acetamide:**

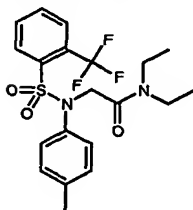
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and  
4-ethyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.03 min, 389 (*M*+1, ES+).

**Example 10:*****N,N*-Diethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

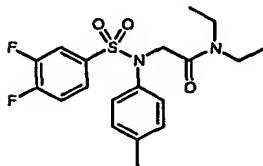
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and toluene-2-sulfonyl chloride

LC-MS: *rt* = 0.98 min, 375 (*M*+1, ES+).

**Example 11:*****N,N*-Diethyl-2-[*p*-tolyl-(2-trifluoromethyl-benzenesulfonyl)-amino]-acetamide:**

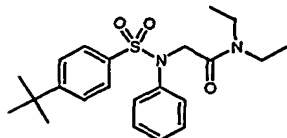
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and 2-trifluoromethyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.00 min, 429 (*M*+1, ES+).

**Example 12:****2-[(3,4-Difluoro-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide:**

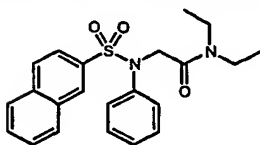
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-toluidine and 3,4-difluoro-benzenesulfonyl chloride

LC-MS: *rt* = 1.00 min, 397 (*M*+1, ES+).

**Example 13:****2-[(4-tert-Butyl-benzenesulfonyl)-phenyl-amino]-N,N-diethyl-acetamide:**

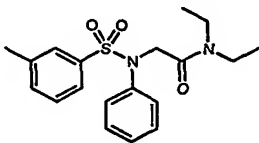
prepared by reaction of 2-bromoacetyl bromide with diethylamine, aniline and  
4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.07 min, 403 (M+1, ES+).

**Example 14:****N,N-Diethyl-2-[(naphthalene-2-sulfonyl)-phenyl-amino]-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine, aniline and  
naphthalene-2-sulfonyl chloride

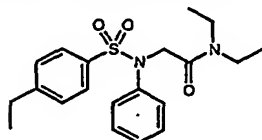
LC-MS: rt = 1.00 min, 397 (M+1, ES+).

**Example 15:****N,N-Diethyl-2-[phenyl-(toluene-3-sulfonyl)-amino]-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine, aniline and  
toluene-3-sulfonyl chloride

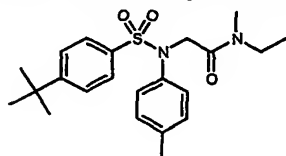
LC-MS: rt = 0.94 min, 361 (M+1, ES+).



**Example 16:*****N,N*-Diethyl-2-[(4-ethyl-benzenesulfonyl)-phenyl-amino]-acetamide:**

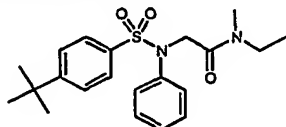
prepared by reaction of 2-bromoacetyl bromide with diethylamine, aniline and  
4-ethyl-benzenesulfonyl chloride

LC-MS: *rt* = 0.99 min, 375 (*M*+1, ES+).

**Example 17:****2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-methyl-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with ethylmethylamine,  
*p*-toluidine and 4-*tert*-butyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.06 min, 403 (*M*+1, ES+).

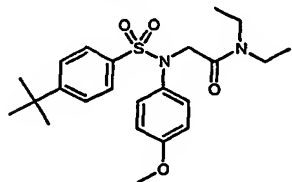
**Example 18:****2-[(4-*tert*-Butyl-benzenesulfonyl)-phenyl-amino]-*N*-ethyl-*N*-methyl-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with ethylmethylamine, aniline  
and 4-*tert*-butyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.02 min, 389 (*M*+1, ES+).

**Example 19:**

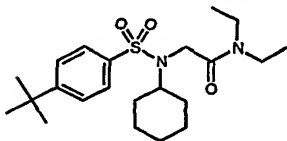
**2-[(4-tert-Butyl-benzenesulfonyl)-(4-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide:**



5 prepared by reaction of 2-bromoacetyl bromide with diethylamine, *p*-anisidine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: *rt* = 1.07 min, 433 (*M*+1, ES+).

**Example 20:**

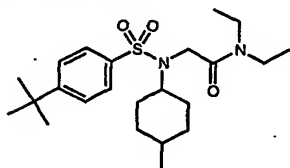
10 **2-[(4-tert-Butyl-benzenesulfonyl)-cyclohexyl-amino]-*N,N*-diethyl-acetamide:**



prepared by reaction of 2-bromoacetyl bromide with diethylamine, cyclohexylamine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: *rt* = 1.16 min, 409 (*M*+1, ES+).

**Example 21:**

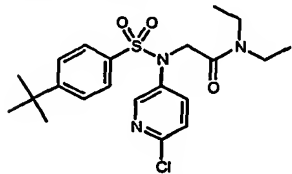
**2-[(4-tert-Butyl-benzenesulfonyl)-(4-methyl-cyclohexyl)-amino]-*N,N*-diethyl-acetamide:**



20 prepared by reaction of 2-bromoacetyl bromide with diethylamine, 4-methyl-cyclohexylamine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: *rt* = 1.20 min, 423 (*M*+1, ES+).

**Example 22:**

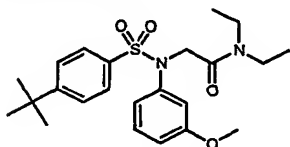
**2-[(4-tert-Butyl-benzenesulfonyl)-(6-chloro-pyridin-3-yl)-amino]-*N,N*-diethyl-acetamide:**



- 5 prepared by reaction of 2-bromoacetyl bromide with diethylamine, 5-amino-2-chloropyridine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.08 min, 438 (M+1, ES+).

**Example 23:**

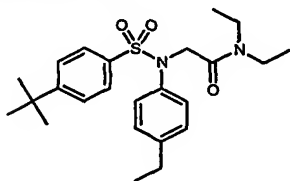
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide:**



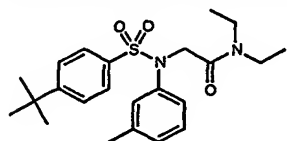
- 10 prepared by reaction of 2-bromoacetyl bromide with diethylamine, *m*-anisidine and 4-tert-butyl-benzenesulfonyl chloride  
15 LC-MS: rt = 1.08 min, 433 (M+1, ES+).

**Example 24:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(4-ethyl-phenyl)-amino]-*N,N*-diethyl-acetamide:**

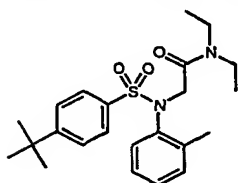


- 20 prepared by reaction of 2-bromoacetyl bromide with diethylamine, 4-ethylaniline and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.15 min, 431 (M+1, ES+).

**Example 25:****2-[(4-tert-Butyl-benzenesulfonyl)-*m*-tolyl-amino]-*N,N*-diethyl-acetamide:**

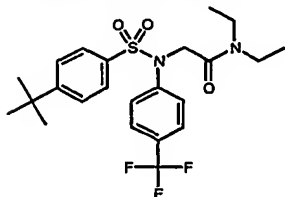
prepared by reaction of 2-bromoacetyl bromide with diethylamine, *m*-toluidine and  
4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.12 min, 417 (M+1, ES+).

**Example 26:****2-[(4-tert-Butyl-benzenesulfonyl)-*o*-tolyl-amino]-*N,N*-diethyl-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine, *o*-toluidine and  
4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.12 min, 417 (M+1, ES+).

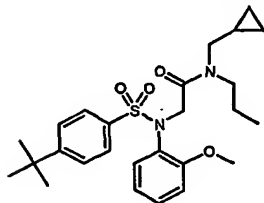
**Example 27:****2-[(4-tert-Butyl-benzenesulfonyl)-(4-trifluoromethyl-phenyl)-amino]-*N,N*-diethyl-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine, 4-trifluoro-  
methyl-aniline and 4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.14 min, 471 (M+1, ES+).

**Example 28:**

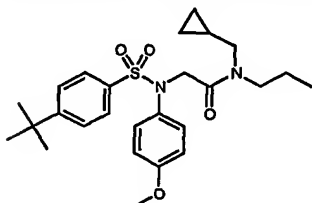
**2-[(4-tert-Butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-cyclopropylmethyl-*N*-propyl-acetamide:**



- 5 prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, *o*-anisidine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.17 min, 473 (M+1, ES+).

**Example 29:**

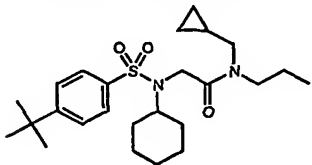
**2-[(4-tert-Butyl-benzenesulfonyl)-(4-methoxy-phenyl)-amino]-*N*-cyclopropylmethyl-*N*-propyl-acetamide:**



- 10 prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, *p*-anisidine and 4-tert-butyl-benzenesulfonyl chloride  
15 LC-MS: rt = 1.16 min, 473 (M+1, ES+).

**Example 30:**

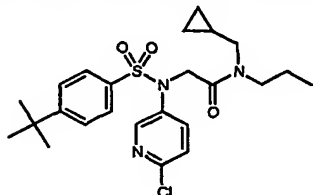
**2-[(4-tert-Butyl-benzenesulfonyl)-cyclohexyl-amino]-*N*-cyclopropylmethyl-*N*-propyl-acetamide:**



- 20 prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, cyclohexylamine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.24 min, 449 (M+1, ES+).

**Example 31:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(6-chloro-pyridin-3-yl)-amino]-*N*-cyclopropylmethyl-*N*-n-propyl-acetamide:**



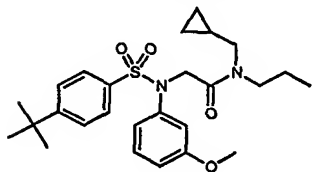
5

prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, 5-amino-2-chloropyridine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.16 min, 478 (M+1, ES+).

10

**Example 32:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-methoxy-phenyl)-amino]-*N*-cyclopropylmethyl-*N*-n-propyl-acetamide:**

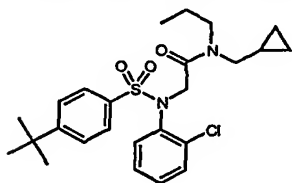


15

prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, *m*-anisidine and 4-tert-butyl-benzenesulfonyl chloride  
LC-MS: rt = 1.17 min, 473 (M+1, ES+).

**Example 33:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(2-chloro-phenyl)-amino]-*N*-cyclopropylmethyl-*N*-n-propyl-acetamide:**



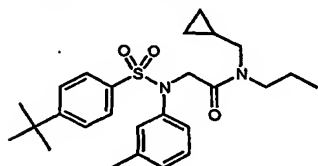
20

prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, 2-chloroaniline and 4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.21 min, 477 (M+1, ES+).

**Example 34:**

**2-[(4-tert-Butyl-benzenesulfonyl)-*m*-tolyl-amino]-*N*-cyclopropylmethyl-*N*-*n*-propyl-acetamide:**

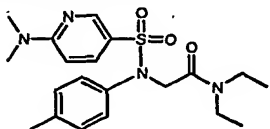


prepared by reaction of 2-bromoacetyl bromide with *N*-cyclopropylmethyl-*N*-propylamine, *m*-toluidine and 4-tert-butyl-benzenesulfonyl chloride

LC-MS: rt = 1.20 min, 457 (M+1, ES+).

**Example 35:**

**2-[(6-Dimethylamino-pyridine-3-sulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide:**

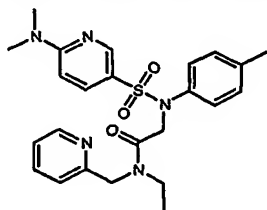


prepared by reaction of 2-bromoacetyl bromide with *N,N*-diethylamine, *p*-toluidine 6-dimethylamino-pyridine-3-sulfonyl chloride; in contrast to the general procedure the intermediate *N,N*-diethyl-2-*p*-tolylamino-acetamide was isolated

LC-MS: rt = 0.87 min, 405 (M+1, ES+).

**Example 36:**

**2-[(6-Dimethylamino-pyridine-3-sulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide:**

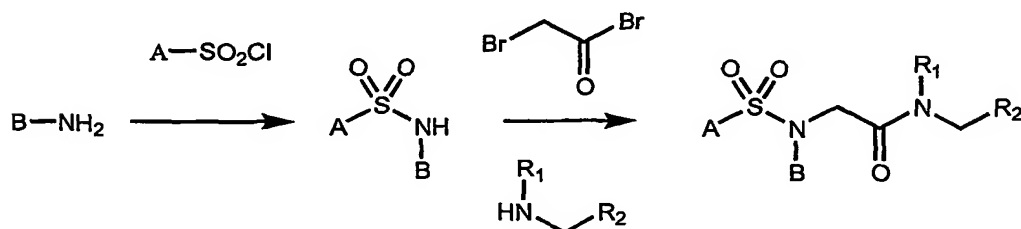


prepared by reaction of 6-dimethylamino-pyridine-3-sulfonyl chloride with *N*-ethyl-*N*-pyridin-2-ylmethyl-2-*p*-tolylamino-acetamide

LC-MS: *rt* = 0.75 min, 468 (*M*+1, ES<sup>+</sup>).

5

### C Synthesis of sulfonylamino-acetic acid derivatives via isolated sulfanilide-intermediates (two step procedure)



10

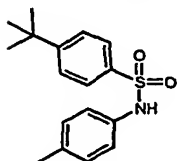
#### C.1 Synthesis of sulfanilide-intermediates (general procedure):

The respective sulfonyl chloride (100 mmol) was added portionwise to a solution of the respective aromatic amine (100 mmol) and ethyldiisopropylamine (120 mmol) in THF (100 mL) at RT. The suspension was stirred for 16 h, the solvent was removed in vacuo and the residue was redissolved in ethyl acetate. After washing the organic phase with water and brine the solvent was removed in vacuo. The residue was purified either by crystallization from diethylether or methanol/water or by preparative HPLC chromatography to give the following sulfonamides:

15

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#### 4-*tert*-Butyl-*N*-*p*-tolyl-benzenesulfonamide:

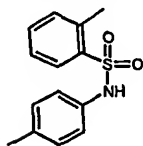


prepared by reaction of *p*-toluidine with 4-*tert*-butyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.18 min, 304 (*M*+1, ES<sup>+</sup>).

25

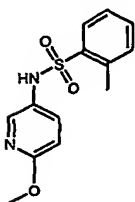


**2-Methyl-N-p-tolyl-benzenesulfonamide:**

prepared by reaction of *p*-toluidine with 2-methyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.06 min, 523 (2M+1, ES+).

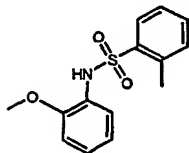
5

**N-(6-Methoxy-pyridin-3-yl)-2-methyl-benzenesulfonamide:**

prepared by reaction of 6-methoxy-pyridin-3-ylamine with 2-methyl-benzenesulfonyl chloride

LC-MS: *rt* = 0.85 min, 279 (M+1, ES+).

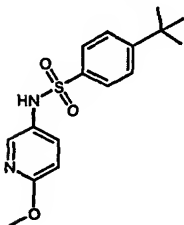
10

**N-(2-Methoxy-phenyl)-2-methyl-benzenesulfonamide:**

prepared by reaction of *o*-anisidine with 2-methyl-benzenesulfonyl chloride

LC-MS: *rt* = 0.93 min, 278 (M+1, ES+).

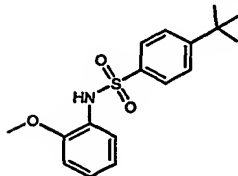
15

**4-tert-Butyl-N-(6-methoxy-pyridin-3-yl)-benzenesulfonamide:**

prepared by reaction of 6-methoxy-pyridin-3-ylamine with 4-tert-butyl-benzenesulfonyl chloride

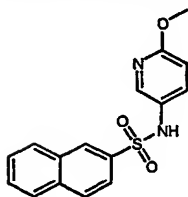
LC-MS: *rt* = 0.96 min, 321 (M+1, ES+).

20

**4-tert-Butyl-N-(2-methoxy-phenyl)-benzenesulfonamide:**

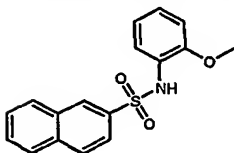
prepared by reaction of *o*-anisidine with 4-tert-butyl-benzenesulfonyl chloride

5 LC-MS: *rt* = 1.02 min, 320 (*M*+1, ES+).

**Naphthalene-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide:**

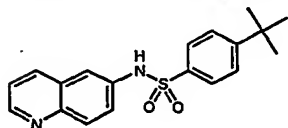
10 prepared by reaction of 6-methoxy-pyridin-3-ylamine with naphthalene-2-sulfonyl chloride

LC-MS: *rt* = 0.91 min, 315 (*M*+1, ES+).

**Naphthalene-2-sulfonic acid (2-methoxy-phenyl)-amide:**

15 prepared by reaction of *o*-anisidine with naphthalene-2-sulfonyl chloride

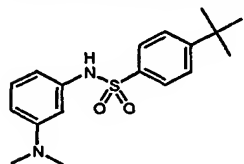
LC-MS: *rt* = 0.97 min, 314 (*M*+1, ES+).

**4-tert-Butyl-N-quinolin-6-yl-benzenesulfonamide:**

20 prepared by reaction of quinolin-6-ylamine with 4-tert-butyl-benzenesulfonyl chloride

LC-MS:  $rt = 0.82$  min, 341 (M+1, ES+).

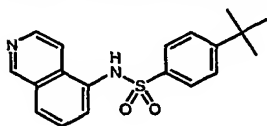
**4-tert-Butyl-N-(3-dimethylamino-phenyl)-benzenesulfonamide:**



5 prepared by reaction of *N,N*-dimethyl-benzene-1,3-diamine with 4-tert-butyl-benzenesulfonyl chloride

LC-MS:  $rt = 0.89$  min, 333 (M+1, ES+).

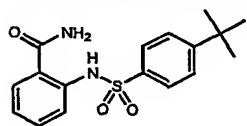
**4-tert-Butyl-N-isoquinolin-5-yl-benzenesulfonamide:**



10 prepared by reaction of isoquinolin-5-ylamine with 4-tert-butyl-benzenesulfonyl chloride

LC-MS:  $rt = 0.80$  min, 341 (M+1, ES+).

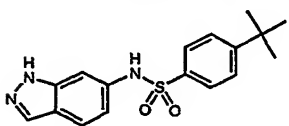
**2-(4-tert-Butyl-benzenesulfonylamino)-benzamide:**



15 prepared by reaction of 2-amino-benzamide with 4-tert-butyl-benzenesulfonyl chloride

LC-MS:  $rt = 0.96$  min, 333 (M+1, ES+).

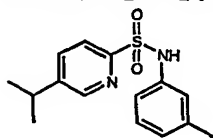
**4-tert-Butyl-N-(1H-indazol-6-yl)-benzenesulfonamide:**



20 prepared by reaction of 1H-indazol-6-ylamine with 4-tert-butyl-benzenesulfonyl chloride

LC-MS:  $rt = 0.93$  min, 330 ( $M+1$ , ES+).

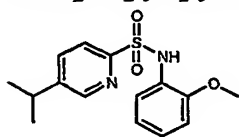
**5-Isopropyl-pyridine-2-sulfonic acid m-tolylamide:**



5 prepared by reaction of m-tolylamine with 5-isopropyl-pyridine-2-sulfonyl chloride

LC-MS:  $rt = 0.96$  min, 291 ( $M+1$ , ES+).

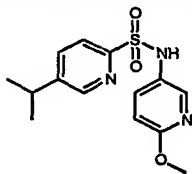
**5-Isopropyl-pyridine-2-sulfonic acid (2-methoxy-phenyl)-amide:**



10 prepared by reaction of 2-methoxy-phenylamine with 5-isopropyl-pyridine-2-sulfonyl chloride

LC-MS:  $rt = 0.94$  min, 307 ( $M+1$ , ES+).

**5-Isopropyl-pyridine-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide:**

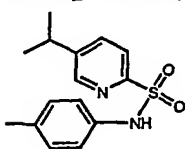


15 prepared by reaction of 6-methoxy-pyridin-3-ylamine with 5-isopropyl-pyridine-2-sulfonyl chloride

LC-MS:  $rt = 0.89$  min, 308 ( $M+1$ , ES+).

20

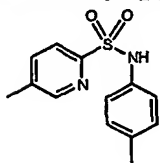
**5-Isopropyl-pyridine-2-sulfonic acid p-tolylamide:**



prepared by reaction of p-tolylamine with 5-isopropyl-pyridine-2-sulfonyl chloride

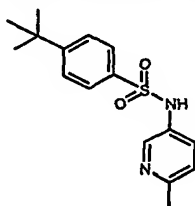
LC-MS:  $rt = 0.97$  min, 291 (M+1, ES+).

**5-Methyl-pyridine-2-sulfonic acid p-tolylamide:**



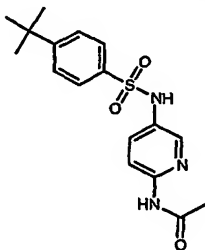
- 5 prepared by reaction of p-tolylamine with 5-methyl-pyridine-2-sulfonyl chloride  
LC-MS:  $rt = 0.88$  min, 263 (M+1, ES+).

**4-tert-Butyl-N-(6-methyl-pyridin-3-yl)-benzenesulfonamide:**

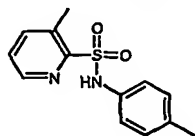


- 10 prepared by reaction of 6-methyl-pyridin-3-ylamine with 4-tert-butyl-benzene-sulfonyl chloride  
LC-MS:  $rt = 0.78$  min, 305 (M+1, ES+).

**N-[5-(4-tert-Butyl-benzenesulfonylamino)-pyridin-2-yl]-acetamide:**

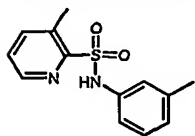


- 15 prepared by reaction of N-(5-amino-pyridin-2-yl)-acetamide with 4-tert-butyl-benzene-sulfonyl chloride  
LC-MS:  $rt = 0.90$  min, 348 (M+1, ES+).

**3-Methyl-pyridine-2-sulfonic acid p-tolylamide:**

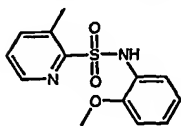
prepared by reaction of p-tolylamine with 3-methyl-pyridine-2-sulfonyl chloride  
LC-MS: rt = 0.89 min, 263 (M+1, ES+).

5

**3-Methyl-pyridine-2-sulfonic acid m-tolylamide:**

prepared by reaction of m-tolylamine with 3-methyl-pyridine-2-sulfonyl chloride  
LC-MS: rt = 0.89 min, 263 (M+1, ES+).

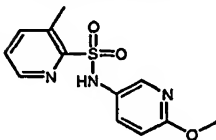
10

**3-Methyl-pyridine-2-sulfonic acid (2-methoxy-phenyl)-amide:**

prepared by reaction of 2-methoxy-phenylamine with 3-methyl-pyridine-2-sulfonyl chloride

15

LC-MS: rt = 0.85 min, 279 (M+1, ES+).

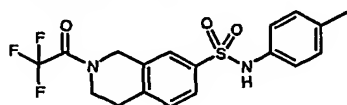
**3-Methyl-pyridine-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide:**

prepared by reaction of 6-methoxy-pyridin-3-ylamine with 3-methyl-pyridine-2-sulfonyl chloride

20

LC-MS: rt = 0.79 min, 280 (M+1, ES+).

**2-(2,2,2-Trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid p-tolylamide:**



prepared by reaction of p-tolylamine with 2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl chloride

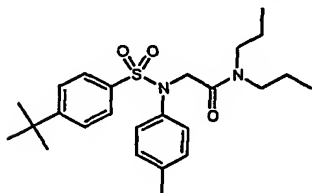
LC-MS: rt = 0.98 min, 399 (M+1, ES+).

**C.2 Synthesis of sulfonylamino-acetic acid derivatives (general procedure):**

To a solution of 2-bromoacetyl bromide (0.20 mmol) in THF (1.0 mL) was added a solution of the respective amine (0.20 mmol) in THF (0.50 mL) at RT. A solution of potassium tert-butoxide (0.20 mmol) in THF (0.50 mL) was added and the reaction mixture was stirred for 2 h. To this suspension a solution of the respective potassium *N*-tolylsulfonamide was added, which was obtained by adding potassium tert-butoxide (0.20 mmol) to a solution of the respective sulfonamide (0.20 mmol) in THF (2.5 mL) and diluting with DMSO (0.50 mL). The obtained suspension was stirred at 60°C for 1 h, the solvent was removed in vacuo and the residue was purified by preparative HPLC chromatography to give the following sulfonamides:

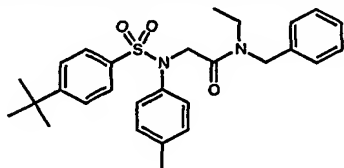
**Example 37:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-di-*n*-propyl-acetamide:**



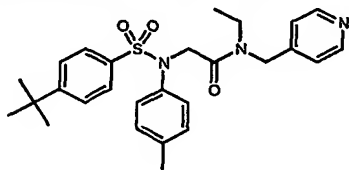
prepared by reaction of 2-bromoacetyl bromide with di-*n*-propylamine and 4-tert-butyl-*N*-p-tolyl-benzenesulfonamide

LC-MS: rt = 1.20 min, 445 (M+1, ES+).

**Example 38:*****N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-acetamide:**

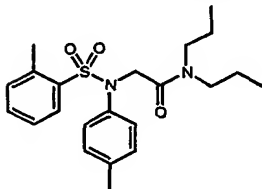
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and  
 4-*tert*-butyl-*N*-*p*-tolyl-benzenesulfonamide

LC-MS: *rt* = 1.19 min, 479 (*M*+1, ES+).

**Example 39:****2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-4-ylmethyl-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with *N*-ethyl-*N*-pyridin-4-ylmethylamine and 4-*tert*-butyl-*N*-*p*-tolyl-benzenesulfonamide

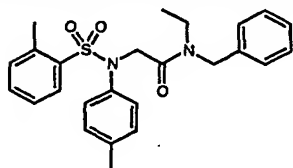
LC-MS: *rt* = 0.83 min, 480 (*M*+1, ES+).

**Example 40:*****N,N*-Di-*n*-propyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with di-*n*-propylamine and 2-methyl-*N*-*p*-tolyl-benzenesulfonamide

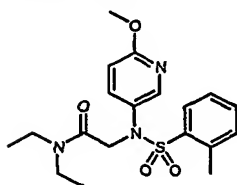
LC-MS: *rt* = 1.20 min, 403 (*M*+1, ES+).



**Example 41:*****N*-Benzyl-*N*-ethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

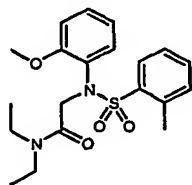
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and  
 2-methyl-*N*-*p*-tolyl-benzenesulfonamide

LC-MS: *rt* = 1.20 min, 437 (*M*+1, ES+).

**Example 42:*****N,N*-Diethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine and *N*-(6-methoxy-pyridin-3-yl)-2-methyl-benzenesulfonamide

LC-MS: *rt* = 0.93 min, 392 (*M*+1, ES+).

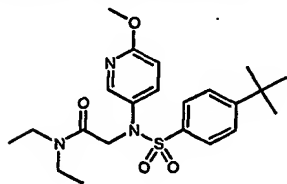
**Example 43:*****N,N*-Diethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**

prepared by reaction of 2-bromoacetyl bromide with diethylamine and  
*N*-(2-methoxy-phenyl)-2-methyl-benzenesulfonamide

LC-MS: *rt* = 0.96 min, 391 (*M*+1, ES+).

**Example 44:**

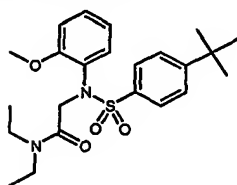
**2-[(4-tert-Butyl-benzenesulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N,N*-diethyl-acetamide:**



- 5 prepared by reaction of 2-bromoacetyl bromide with diethylamine and 4-tert-butyl-*N*-(6-methoxy-pyridin-3-yl)-benzenesulfonamide  
LC-MS:  $rt = 1.02 \text{ min}$ , 434 ( $M+1$ ,  $ES^+$ ).

**Example 45:**

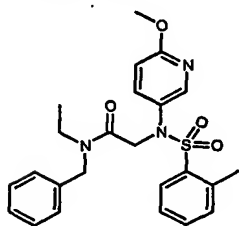
- 10 **2-[(4-tert-Butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide:**



- 15 prepared by reaction of 2-bromoacetyl bromide with diethylamine and 4-tert-butyl-*N*-(2-methoxy-phenyl)-benzenesulfonamide  
LC-MS:  $rt = 1.04 \text{ min}$ , 433 ( $M+1$ ,  $ES^+$ ).

**Example 46:**

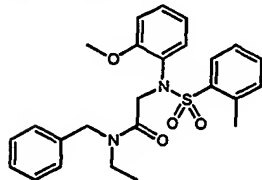
***N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 20 prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and *N*-(6-methoxy-pyridin-3-yl)-2-methyl-benzenesulfonamide  
LC-MS:  $rt = 1.01 \text{ min}$ , 454 ( $M+1$ ,  $ES^+$ ).

**Example 47:**

***N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



5

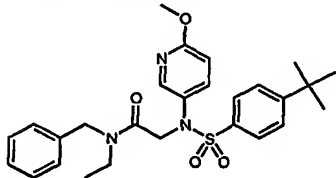
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and *N*-(2-methoxy-phenyl)-2-methyl-benzenesulfonamide

LC-MS: *rt* = 1.04 min, 453 (*M*+1, ES+).

10

**Example 48:**

***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-ethyl-acetamide:**



15

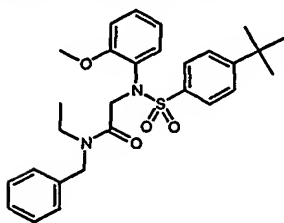
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and 4-*tert*-butyl-*N*-(6-methoxy-pyridin-3-yl)-benzenesulfonamide

LC-MS: *rt* = 1.08 min, 496 (*M*+1, ES+).

**Example 49:**

***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-ethyl-acetamide:**

20



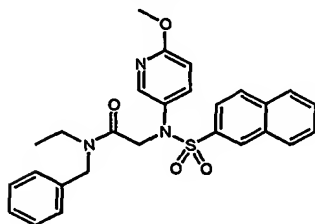
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and 4-*tert*-butyl-*N*-(2-methoxy-phenyl)-benzenesulfonamide

LC-MS: *rt* = 1.10 min, 495 (M+1, ES+).

5

### Example 50:

***N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(naphthalene-2-sulfonyl)-amino]-acetamide:**



prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and naphthalene-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide

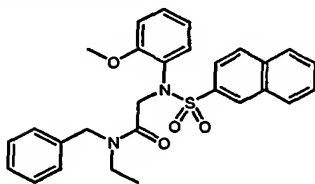
10

LC-MS: *rt* = 1.05 min, 490 (M+1, ES+).

### Example 51:

***N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(naphthalene-2-sulfonyl)-amino]-acetamide:**

15



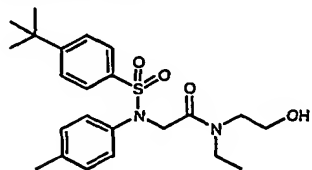
prepared by reaction of 2-bromoacetyl bromide with *N*-benzyl-*N*-ethylamine and naphthalene-2-sulfonic acid (2-methoxy-phenyl)-amide

LC-MS: *rt* = 1.06 min, 489 (M+1, ES+).

20

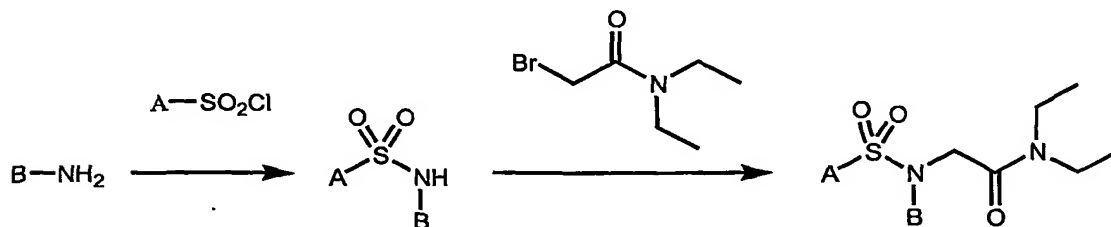
**Example 52:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(2-hydroxy-ethyl)-acetamide:**



prepared by reaction of 2-bromoacetyl bromide with *N*-ethyl-*N*-(2-hydroxy-ethyl)-amine and 4-tert-butyl-*N*-p-tolyl-benzenesulfonamide; in contrast to the general procedure the intermediate 2-bromo-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide was isolated before being used in the coupling with the potassium *N*-tolylsulfonamide. LC-MS: *rt* = 0.97 min, 433 (*M*+1, ES+).

**D Synthesis of sulfonylamino-acetic acid derivatives via isolated 2-bromo-*N,N*-diethylacetamide (two step procedure)**



**D.1 Synthesis of 2-bromo-*N,N*-diethylacetamide :**

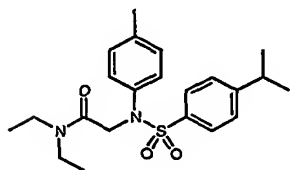
A solution of 2-bromoacetyl bromide (20.2 g, 100 mmol) in THF (300 mL) was cooled to 0°C and treated with diethylamine (7.31 g, 100 mmol). After dropwise addition of ethyldiisopropylamine (15.5 g, 120 mmol) the reaction mixture was allowed to reach RT and was stirred for 90 min. Water (250 mL) and ethyl acetate (300 mL) were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate (100 mL). The solvents were removed in vacuo and the residue was purified by distillation (bp 120 - 121°C / 24 mbar) to give 5.24 g (27%) of the title compound as pale yellow oil.

## D.2 Synthesis of sulfonylamino-acetic acid derivatives (general procedure):

A solution of the respective sulfonyl chloride (0.20 mmol) in DCM (1.0 mL) was added to a solution of *p*-toluidine (0.20 mmol) and ethyldiisopropylamine (0.24 mmol) in DCM (1.0 mL) at RT. After stirring for 16 h water was added, the layers were separated and the aqueous layer was extracted twice with DCM (2.0 mL). The combined organic extracts were concentrated in vacuo and dissolved in dry THF (1.0 mL). A solution of potassium tert-butoxide (0.20 mmol) in THF (0.50 mL) was added. The reaction mixture was treated with a solution of 2-bromo-*N,N*-diethylacetamide (0.20 mmol) in THF (0.50 mL) and stirred for 16 h at RT. The solvent was removed in vacuo and the residue was purified by preparative HPLC chromatography to give the following sulfonamides:

### Example 53:

*N,N*-Diethyl-2-[(4-isopropyl-benzenesulfonyl)-*p*-tolyl-amino]-acetamide:

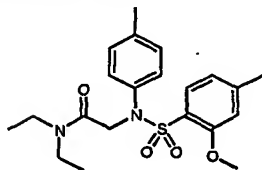


prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and 4-isopropyl-benzenesulfonyl chloride

LC-MS: *rt* = 1.04 min, 403 (*M*+1, ES+).

### Example 54:

*N,N*-Diethyl-2-[(2-methoxy-4-methyl-benzenesulfonyl)-*p*-tolyl-amino]-acetamide:

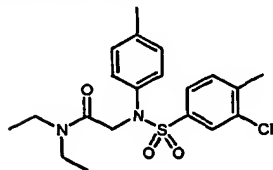


prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and 2-methoxy-4-methyl-benzenesulfonyl chloride

LC-MS: *rt* = 0.96 min, 405 (*M*+1, ES+).

**Example 55:**

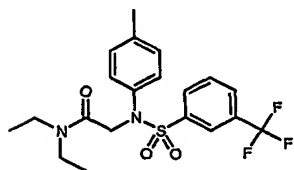
**2-[(3-Chloro-4-methyl-benzenesulfonyl)-p-tolyl-amino]-*N,N*-diethyl-acetamide:**



- 5 prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and 3-chloro-4-methyl-benzenesulfonyl chloride  
LC-MS: rt = 1.03 min, 409 (M+1, ES+).

**Example 56:**

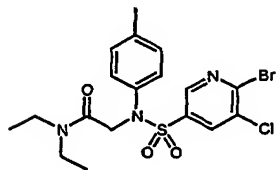
***N,N*-Diethyl-2-[p-tolyl-(3-trifluoromethyl-benzenesulfonyl)-amino]-acetamide:**



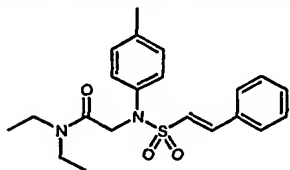
- 10 prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and 3-trifluoromethyl-benzenesulfonyl chloride  
15 LC-MS: rt = 1.03 min, 429 (M+1, ES+).

**Example 57:**

**2-[(6-Bromo-5-chloro-pyridine-3-sulfonyl)-p-tolyl-amino]-*N,N*-diethyl-acetamide:**

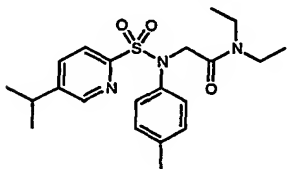


- 20 prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and 6-bromo-5-chloro-pyridine-3-sulfonyl chloride  
LC-MS: rt = 1.04 min, 474 (M+1, ES+).

**Example 58:*****N,N*-Diethyl-2-[(*E*)-2-phenyl-ethenesulfonyl]-*p*-tolyl-amino]-acetamide:**

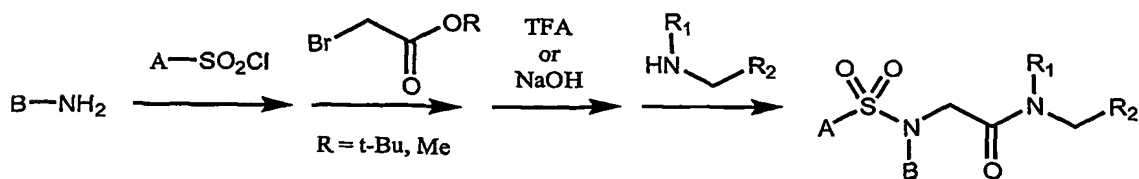
prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and  
 (E)-2-phenyl-ethenesulfonyl chloride

LC-MS: *rt* = 1.01 min, 387 (M+1, ES+).

**Example 59:*****N,N*-Diethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

prepared by reaction of 2-bromo-*N,N*-diethylacetamide with *p*-toluidine and  
 5-isopropyl-pyridine-2-sulfonyl chloride; in contrast to the general procedure the  
 intermediate 5-isopropyl-pyridine-2-sulfonic acid *p*-tolylamide was isolated and  
 crystallized from methanol/water 10/1

LC-MS: *rt* = 1.00 min, 404 (M+1, ES+).

**E Synthesis of sulfonylamino-acetic acid derivatives via an amide coupling**

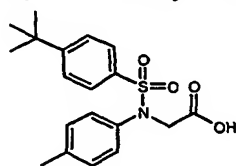


### E.1 Synthesis of sulfonylamino-acetic acids via tert-butyl acetates (general procedure):

A solution of the respective sulfonamide A-S(O)<sub>2</sub>NH-B (1.6 mmol) in DMSO (5.0 mL) was added to solid potassium tert-butoxide (1.6 mmol) which was dissolved by ultrasound. Tert-butyl bromoacetate (1.69 mmol, 0.25 mL) was added and the reaction mixture was stirred at RT for 12 h. Water (20 mL) and ethyl acetate (15 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (15 mL). The solvents were removed in vacuo and the residue was either purified by preparative HPLC chromatography or used without further purification.

A solution of the obtained tert-butyl acetate in DCM (5.0 mL) was treated with TFA (1.6 mL) and stirred for 12 h at 35°C. Water (10 mL) and ethyl acetate (20 mL) were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate (2 x 20 mL). The solvents were removed in vacuo and the residue was purified by preparative HPLC chromatography to give the following acetic acid derivatives:

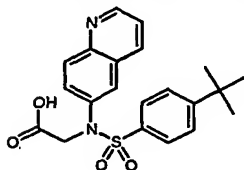
#### [(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid:



prepared by reaction of 4-tert-butyl-N-p-tolyl-benzenesulfonamide with tert-butyl bromoacetate

LC-MS: *rt* = 0.99 min, 362 (M+1, ES+).

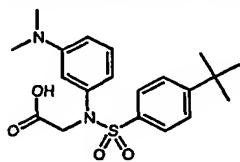
#### [(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid:



prepared by reaction of 4-tert-butyl-N-quinolin-6-yl-benzenesulfonamide with tert-butyl bromoacetate

LC-MS:  $rt = 0.84$  min, 399 ( $M+1$ , ES+).

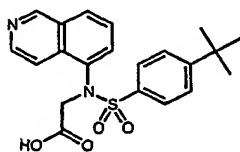
**[(4-*tert*-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid:**



5 prepared by reaction of 4-*tert*-butyl-*N*-(3-dimethylamino-phenyl)-benzenesulfonamide with *tert*-butyl bromoacetate

LC-MS:  $rt = 0.90$  min, 391 ( $M+1$ , ES+).

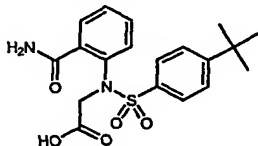
**[(4-*tert*-Butyl-benzenesulfonyl)-isoquinolin-5-yl-amino]-acetic acid:**



10 prepared by reaction of 4-*tert*-butyl-*N*-isoquinolin-5-yl-benzenesulfonamide with *tert*-butyl bromoacetate

LC-MS:  $rt = 0.80$  min, 399 ( $M+1$ , ES+).

15 **[(4-*tert*-Butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid:**

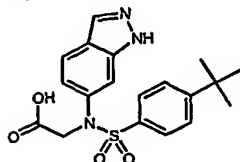


prepared by reaction of 2-(4-*tert*-butyl-benzenesulfonylamino)-benzamide with *tert*-butyl bromoacetate

LC-MS:  $rt = 0.88$  min, 391 ( $M+1$ , ES+).

20

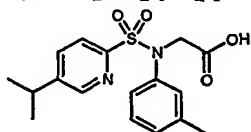
**[(4-*tert*-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-acetic acid:**



prepared by reaction of 4-tert-butyl-*N*-(1H-indazol-6-yl)-benzenesulfonamide with tert-butyl bromoacetate

LC-MS: *rt* = 0.91 min, 388 (*M*+1, ES+).

5 **[(5-Isopropyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid:**

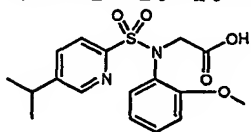


prepared by reaction of 5-isopropyl-pyridine-2-sulfonic acid *m*-tolylamide with tert-butyl bromoacetate

LC-MS: *rt* = 0.94 min, 349 (*M*+1, ES+).

10

**[(5-Isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetic acid:**

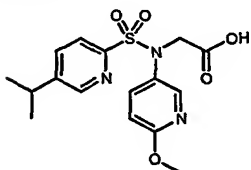


prepared by reaction of 5-isopropyl-pyridine-2-sulfonic acid (2-methoxy-phenyl)-amide with tert-butyl bromoacetate

LC-MS: *rt* = 0.89 min, 365 (*M*+1, ES+).

15

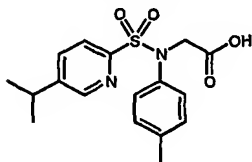
**[(5-Isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetic acid:**



prepared by reaction of 5-isopropyl-pyridine-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide with tert-butyl bromoacetate

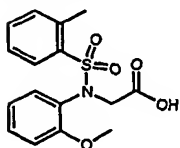
LC-MS: *rt* = 0.87 min, 366 (*M*+1, ES+).

20

**[(5-Isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid:**

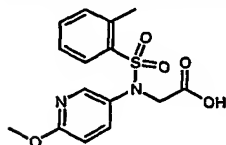
prepared by reaction of 5-isopropyl-pyridine-2-sulfonic acid p-tolylamide with tert-butyl bromoacetate

5 LC-MS:  $r_t = 0.93$  min, 349 (M+1, ES+).

**[(2-Methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid:**

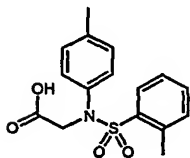
prepared by reaction of *N*-(2-methoxy-phenyl)-2-methyl-benzenesulfonamide with tert-butyl bromoacetate

10 LC-MS:  $r_t = 0.89$  min, 336 (M+1, ES+).

**[(6-Methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid:**

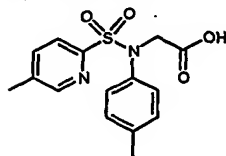
prepared by reaction of *N*-(6-methoxy-pyridin-3-yl)-2-methyl-benzenesulfonamide with tert-butyl bromoacetate

15 LC-MS:  $r_t = 0.85$  min, 337 (M+1, ES+).

**[(Toluene-2-sulfonyl)-p-tolyl-amino]-acetic acid:**

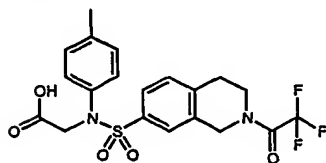
prepared by reaction of 2-methyl-*N*-p-tolyl-benzenesulfonamide with tert-butyl bromoacetate

20 LC-MS:  $r_t = 0.91$  min, 320 (M+1, ES+).

**[(5-Methyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid:**

prepared by reaction of 5-methyl-pyridine-2-sulfonic acid p-tolylamide with tert-butyl bromoacetate

5 LC-MS: rt = 0.85 min, 321 (M+1, ES+).

**{p-Tolyl-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl]-amino}-acetic acid:**

10 prepared by reaction of 2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid p-tolylamide with tert-butyl bromoacetate

LC-MS: rt = 0.95 min, 457 (M+1, ES+).

15

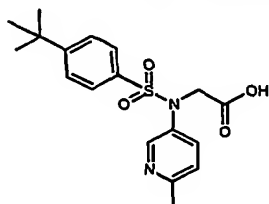
**E.2 Synthesis of sulfonylamino-acetic acids via methyl acetates (general procedure):**

A solution of the respective sulfonamide A-S(O)<sub>2</sub>NH-B (10.0 mmol) in DMSO (10.0 mL) was treated with solid potassium tert-butoxide (10.0 mmol). Methyl bromoacetate (11.0 mmol, 1.0 mL) was added at RT and the reaction mixture was heated to 60°C for 4 h. Water (40 mL) and ethyl acetate (40 mL) were added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (4 x 50 mL) and brine (50 mL) and the solvents were removed in vacuo.

25 A solution of NaOH (100 mmol) in water (50 mL) was added to a solution of the crude methyl acetate in methanol (500 mL) and stirred either at 60°C for 1 h or at RT for 16 h. Hydrochloric acid (2.0 mol/L) was added to pH 7 and methanol was removed in vacuo. The aqueous layer was extracted with ethyl acetate (4 x 100 mL) and the combined organic layers were washed with brine (50 mL). The solvents were

removed in vacuo and the residue was purified by preparative HPLC chromatography to give the following acetic acid derivatives:

**[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid:**



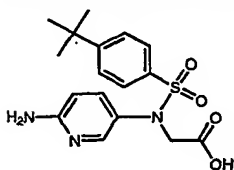
5

prepared by reaction of 4-tert-butyl-*N*-(6-methyl-pyridin-3-yl)-benzenesulfonamide with methyl bromoacetate

LC-MS: *rt* = 0.80 min, 363 (*M*+1, ES+).

10

**[(6-Amino-pyridin-3-yl)-(4-tert-butyl-benzenesulfonyl)-amino]-acetic acid:**

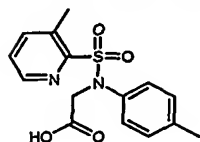


prepared by reaction of *N*-[5-(4-tert-butyl-benzenesulfonylamino)-pyridin-2-yl]-acetamide with methyl bromoacetate

LC-MS: *rt* = 0.74 min, 364 (*M*+1, ES+).

15

**[(3-Methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid:**

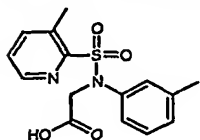


prepared by reaction of 3-methyl-pyridine-2-sulfonic acid *p*-tolylamide with methyl bromoacetate

20

LC-MS: *rt* = 0.85 min, 321 (*M*+1, ES+).

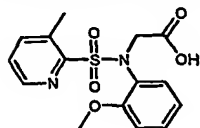
**[(3-Methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid:**



prepared by reaction of 3-methyl-pyridine-2-sulfonic acid m-tolylamide with methyl bromoacetate

LC-MS:  $r_t = 0.85$  min, 321 ( $M+1$ , ES+).

5 **[(2-Methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid:**

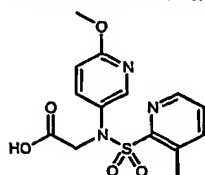


prepared by reaction of 3-methyl-pyridine-2-sulfonic acid (2-methoxy-phenyl)-amide with methyl bromoacetate

LC-MS:  $r_t = 0.80$  min, 337 ( $M+1$ , ES+).

10

**[(6-Methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid:**



prepared by reaction of 3-methyl-pyridine-2-sulfonic acid (6-methoxy-pyridin-3-yl)-amide with methyl bromoacetate

LC-MS:  $r_t = 0.80$  min, 338 ( $M+1$ , ES+).

15

E.3 **Synthesis of sulfonylamino-acetic acids (TBTU coupling, general procedure):**

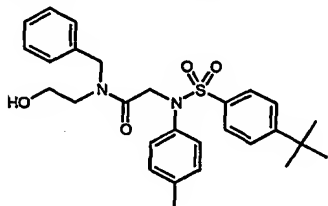
20

A solution of the respective acetic acid derivative (0.10 mmol) in DMF (1.0 mL) was treated with the respective amine (0.10 mmol). DIPEA (0.30 mmol) and TBTU (0.13 mmol) were added. The reaction mixture was stirred at RT for 16 h and purified by preparative HPLC chromatography to give the following sulfonamides:

25

**Example 60:**

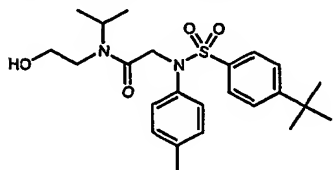
***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-hydroxy-ethyl)-acetamide:**



- 5 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-acetic acid with 2-benzylamino-ethanol  
LC-MS: *rt* = 1.04 min, 495 (*M*+1, ES+).

**Example 61:**

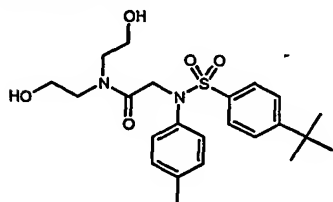
- 10 **2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-hydroxy-ethyl)-*N*-isopropyl-acetamide:**



- 15 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-acetic acid with 2-isopropylamino-ethanol  
LC-MS: *rt* = 1.00 min, 447 (*M*+1, ES+).

**Example 62:**

**2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-bis-(2-hydroxy-ethyl)-acetamide:**

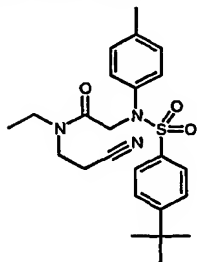


- 20 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-acetic acid with 2-(2-hydroxy-ethylamino)-ethanol  
LC-MS: *rt* = 0.90 min, 449 (*M*+1, ES+).



**Example 63:**

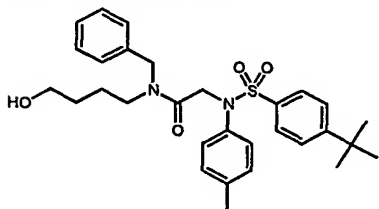
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(2-cyano-ethyl)-N-ethyl-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 3-ethylamino-propionitrile  
LC-MS:  $t_r = 1.04$  min, 442 (M+1, ES+).

**Example 64:**

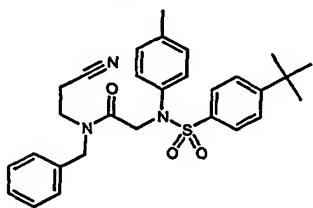
- 10 **N-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-N-(4-hydroxy-butyl)-acetamide:**



- 15 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 4-benzylamino-butan-1-ol  
LC-MS:  $t_r = 1.05$  min, 523 (M+1, ES+).

**Example 65:**

**N-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-N-(2-cyano-ethyl)-acetamide:**



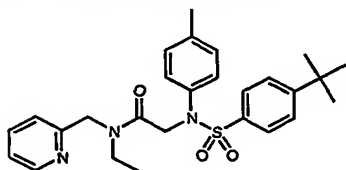
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid  
with 3-benzylamino-propionitrile

LC-MS:  $rt = 1.09$  min, 504 (M+1, ES+).

5

**Example 66:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide:**



prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid  
with ethyl-pyridin-2-ylmethyl-amine

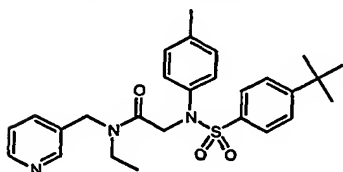
10

LC-MS:  $rt = 0.92$  min, 480 (M+1, ES+).

**Example 67:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-pyridin-3-ylmethyl-acetamide:**

15



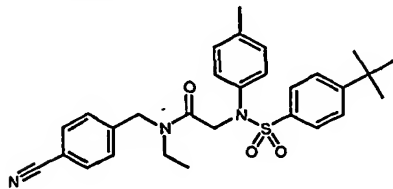
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid  
with ethyl-pyridin-3-ylmethyl-amine

LC-MS:  $rt = 0.88$  min, 480 (M+1, ES+).

20

**Example 68:**

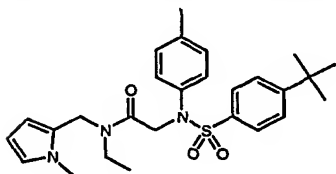
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(4-cyano-benzyl)-N-ethyl-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 4-ethylaminomethyl-benzonitrile  
LC-MS: rt = 1.10 min, 504 (M+1, ES+).

**Example 69:**

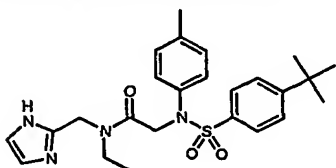
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(1-methyl-1H-pyrrol-2-ylmethyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(1-methyl-1H-pyrrol-2-ylmethyl)-amine  
15 LC-MS: rt = 1.11 min, 482 (M+1, ES+).

**Example 70:**

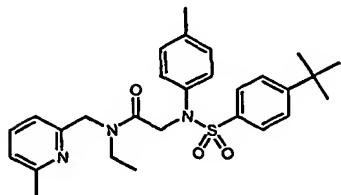
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(1H-imidazol-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(1H-imidazol-2-ylmethyl)-amine  
LC-MS: rt = 0.85 min, 469 (M+1, ES+).

**Example 71:**

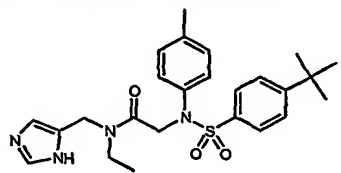
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $rt = 0.90$  min, 494 (M+1, ES+).

**Example 72:**

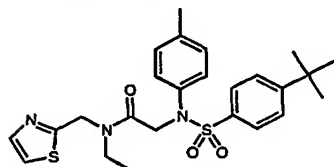
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(3H-imidazol-4-ylmethyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(3H-imidazol-4-ylmethyl)-amine  
15 LC-MS:  $rt = 0.85$  min, 469 (M+1, ES+).

**Example 73:**

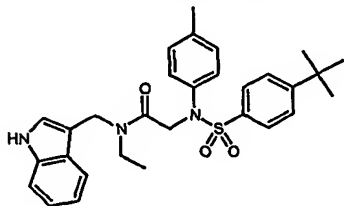
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-thiazol-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS:  $rt = 1.06$  min, 486 (M+1, ES+).

**Example 74:**

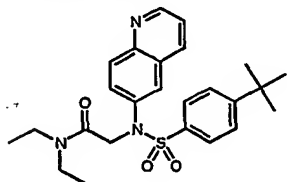
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(1H-indol-3-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(1H-indol-3-ylmethyl)-amine  
LC-MS: rt = 1.09 min, 518 (M+1, ES+).

**Example 75:**

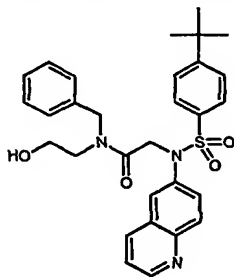
**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N,N-diethyl-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with diethylamine  
15 LC-MS: rt = 0.92 min, 454 (M+1, ES+).

**Example 76:**

**N-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-(2-hydroxy-ethyl)-acetamide:**

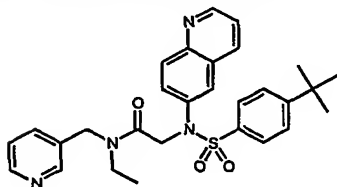


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with 2-benzylamino-ethanol  
 LC-MS: rt = 0.90 min, 532 (M+1, ES+).

5

**Example 77:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-ethyl-N-pyridin-3-ylmethyl-acetamide:**



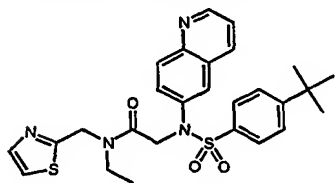
10

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine  
 LC-MS: rt = 0.78 min, 517 (M+1, ES+).

**Example 78:**

15

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-ethyl-N-thiazol-2-ylmethyl-acetamide:**

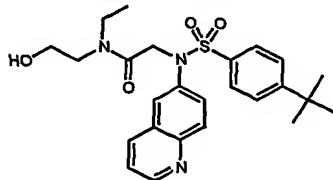


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
 LC-MS: rt = 0.91 min, 523 (M+1, ES+).

20

**Example 79:**

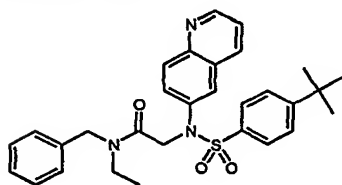
**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with 2-ethylamino-ethanol  
LC-MS:  $t_r = 0.81$  min, 470 ( $M+1$ , ES+).

**Example 80:**

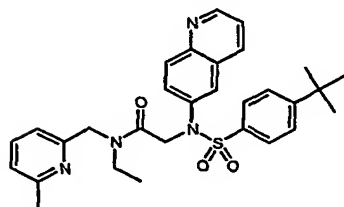
- 10 ***N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-acetamide:**



- 15 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS:  $t_r = 1.00$  min, 516 ( $M+1$ , ES+).

**Example 81:**

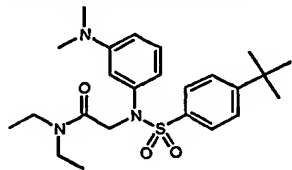
**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $t_r = 0.79$  min, 531 ( $M+1$ , ES+).

**Example 82:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N,N*-diethyl-acetamide:**



5

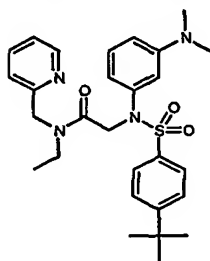
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with diethylamine

LC-MS:  $rt = 0.96$  min, 446 (M+1, ES+).

10

**Example 83:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide:**



prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine

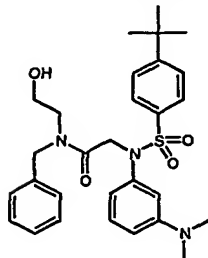
15

LC-MS:  $rt = 0.86$  min, 509 (M+1, ES+).



**Example 84:**

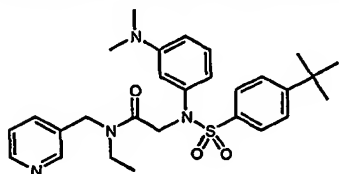
***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-(2-hydroxy-ethyl)-acetamide:**



- 5 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 2-benzylamino-ethanol  
LC-MS: *rt* = 0.95 min, 524 (*M*+1, ES+).

**Example 85:**

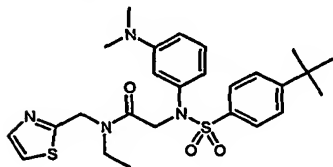
- 10 **2-[(4-*tert*-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-acetamide:**



- 15 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine  
LC-MS: *rt* = 0.82 min, 509 (*M*+1, ES+).

**Example 86:**

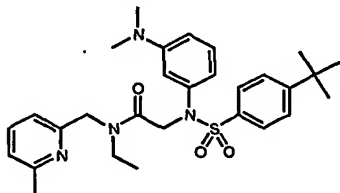
**2-[(4-*tert*-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS: *rt* = 0.96 min, 515 (*M*+1, ES+).

**Example 87:**

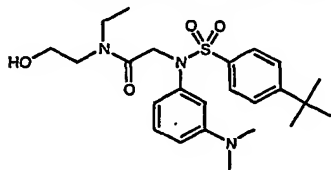
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $rt = 0.85$  min, 523 (M+1, ES+).

**Example 88:**

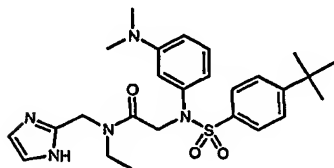
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-(2-hydroxy-ethyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 2-ethylamino-ethanol  
15 LC-MS:  $rt = 0.85$  min, 462 (M+1, ES+).

**Example 89:**

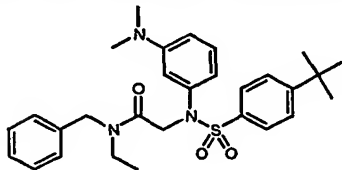
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-(1H-imidazol-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-(1H-imidazol-2-ylmethyl)-amine  
LC-MS:  $rt = 0.80$  min, 498 (M+1, ES+).

**Example 90:**

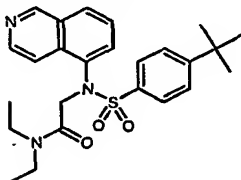
***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-acetamide:**



- 5 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS: *rt* = 1.05 min, 508 (*M*+1, ES+).

**Example 91:**

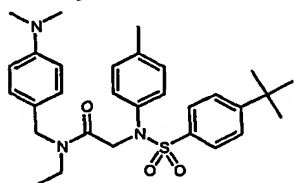
- 10 **2-[(4-*tert*-Butyl-benzenesulfonyl)-isoquinolin-5-yl-amino]-*N,N*-diethyl-acetamide:**



- 15 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-isoquinolin-5-yl-amino]-acetic acid with diethylamine  
LC-MS: *rt* = 0.86 min, 454 (*M*+1, ES+).

**Example 92:**

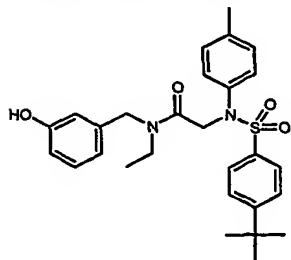
**2-[(4-*tert*-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(4-dimethylamino-benzyl)-*N*-ethyl-acetamide:**



- 20 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-*p*-tolyl-amino]-acetic acid with (4-ethylaminomethyl-phenyl)-dimethyl-amine  
LC-MS: *rt* = 0.93 min, 522 (*M*+1, ES+).

**Example 93:**

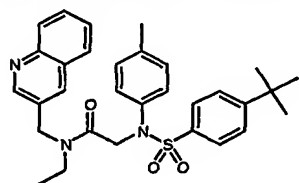
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(3-hydroxy-benzyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 3-ethylaminomethyl-phenol  
LC-MS:  $t_r = 1.05$  min, 495 ( $M+1$ , ES+).

**Example 94:**

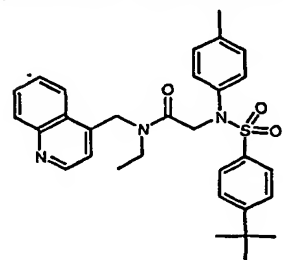
- 10 **2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-quinolin-3-ylmethyl-acetamide:**



- 15 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-quinolin-3-ylmethyl-amine  
LC-MS:  $t_r = 0.96$  min, 530 ( $M+1$ , ES+).

**Example 95:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-quinolin-4-ylmethyl-acetamide:**



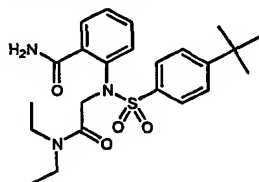
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-quinolin-4-ylmethyl-amine

LC-MS:  $rt = 0.93 \text{ min}$ , 530 (M+1, ES+).

5

### Example 96:

**2-[(4-tert-Butyl-benzenesulfonyl)-diethylcarbamoylmethyl-amino]-benzamide:**



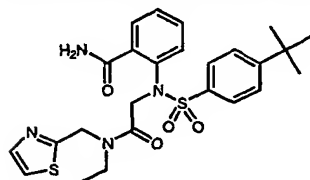
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with diethylamine

LC-MS:  $rt = 0.96 \text{ min}$ , 446 (M+1, ES+).

10

### Example 97:

**2-{(4-tert-Butyl-benzenesulfonyl)-[(ethyl-thiazol-2-ylmethyl-carbamoyl)-methyl]-amino}-benzamide:**



prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine

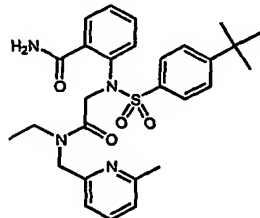
LC-MS:  $rt = 0.94 \text{ min}$ , 515 (M+1, ES+).

15

20

**Example 98:**

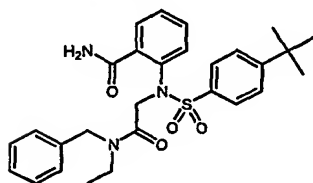
**2-((4-tert-Butyl-benzenesulfonyl)-{ethyl-(6-methyl-pyridin-2-ylmethyl)-carbamoyl}-methyl)-amino)-benzamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $rt = 0.80$  min, 523 ( $M+1$ , ES+).

**Example 99:**

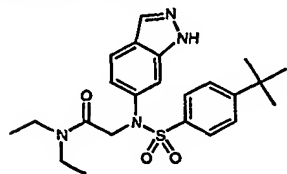
- 10 **2-[[ (Benzyl-ethyl-carbamoyl)-methyl]- (4-tert-butyl-benzenesulfonyl)-amino]-benzamide:**



- 15 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS:  $rt = 1.02$  min, 508 ( $M+1$ , ES+).

**Example 100:**

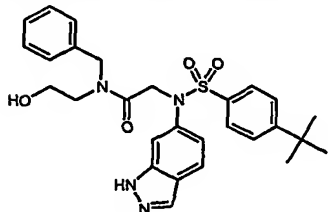
**2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-N,N-diethyl-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-acetic acid with diethylamine  
LC-MS:  $rt = 0.98$  min, 443 ( $M+1$ , ES+).

**Example 101:**

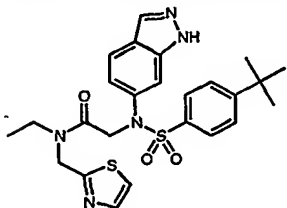
***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-(2-hydroxy-ethyl)-acetamide:**



- 5 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-acetic acid with 2-benzylamino-ethanol  
LC-MS: *rt* = 0.97 min, 521 (*M*+1, ES+).

**Example 102:**

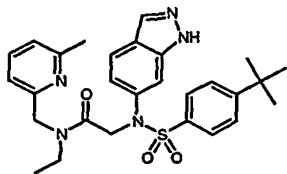
- 10 **2-[(4-*tert*-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-acetamide:**



- 15 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS: *rt* = 0.97 min, 512 (*M*+1, ES+).

**Example 103:**

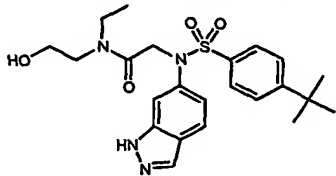
**2-[(4-*tert*-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.75 min, 520 (*M*+1, ES+).

**Example 104:**

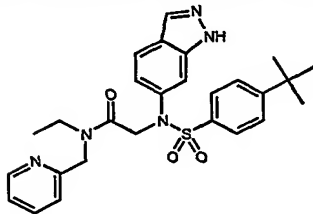
**2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-N-ethyl-N-(2-hydroxy-ethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-acetic acid with 2-ethylamino-ethanol  
LC-MS: rt = 0.82 min, 459 (M+1, ES+).

**Example 105:**

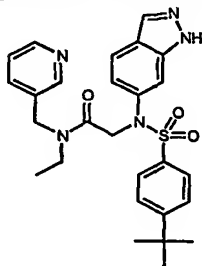
- 10 **2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide:**



- 15 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS: rt = 0.78 min, 506 (M+1, ES+).

**Example 106:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-N-ethyl-N-pyridin-3-ylmethyl-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(1H-indazol-6-yl)-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine

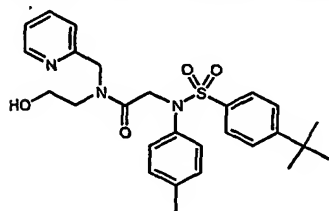


LC-MS:  $rt = 0.81$  min, 506 (M+1, ES+).

**Example 107:**

5

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(2-hydroxy-ethyl)-N-pyridin-2-ylmethyl-acetamide:**



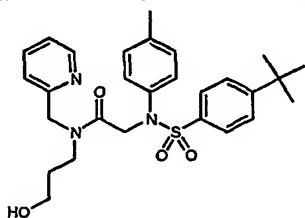
prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol

LC-MS:  $rt = 0.86$  min, 496 (M+1, ES+).

10

**Example 108:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(3-hydroxy-propyl)-N-pyridin-2-ylmethyl-acetamide:**



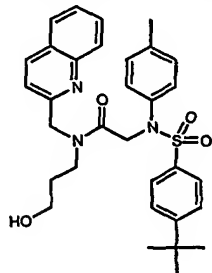
15

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 3-[(pyridin-2-ylmethyl)-amino]-propan-1-ol

LC-MS:  $rt = 0.87$  min, 510 (M+1, ES+).

**Example 109:**

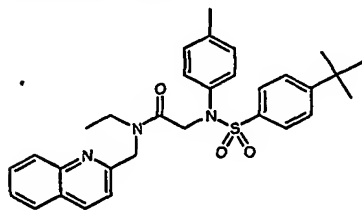
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(3-hydroxy-propyl)-N-quinolin-2-ylmethyl-acetamide:**



prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with 3-[(quinolin-2-ylmethyl)-amino]-propan-1-ol  
LC-MS:  $t_r = 0.95$  min, 560 (M+1, ES+).

**Example 110:**

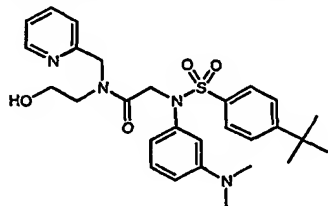
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-quinolin-2-ylmethyl-acetamide:**



prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-quinolin-2-ylmethyl-amine  
LC-MS:  $t_r = 1.01$  min, 530 (M+1, ES+).

**Example 111:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-(2-hydroxy-ethyl)-N-pyridin-2-ylmethyl-acetamide:**

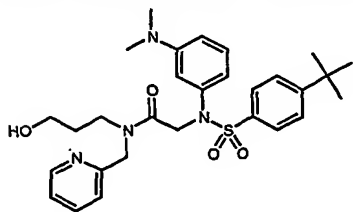


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
LC-MS: rt = 0.80 min, 525 (M+1, ES+).

5

**Example 112:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-(3-hydroxy-propyl)-N-pyridin-2-ylmethyl-acetamide:**



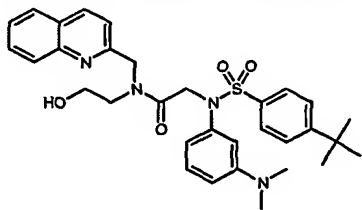
10

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 3-[(pyridin-2-ylmethyl)-amino]-propan-1-ol  
LC-MS: rt = 0.80 min, 539 (M+1, ES+).

**Example 113:**

15

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-(2-hydroxy-ethyl)-N-quinolin-2-ylmethyl-acetamide:**

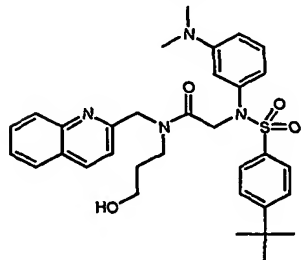


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 2-[(quinolin-2-ylmethyl)-amino]-ethanol.  
LC-MS: rt = 0.89 min, 575 (M+1, ES+).

20

**Example 114:**

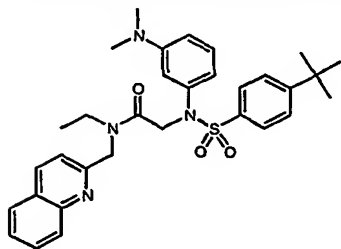
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-(3-hydroxy-propyl)-N-quinolin-2-ylmethyl-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with 3-[(quinolin-2-ylmethyl)-amino]-propan-1-ol  
LC-MS: rt = 0.89 min, 589 (M+1, ES+).

**Example 115:**

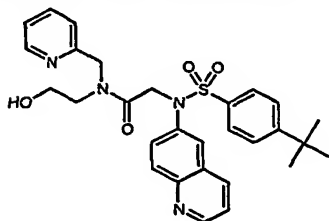
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-quinolin-2-ylmethyl-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with ethyl-quinolin-2-ylmethyl-amine  
15 LC-MS: rt = 0.96 min, 559 (M+1, ES+).

**Example 116:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-(2-hydroxy-ethyl)-N-pyridin-2-ylmethyl-acetamide:**

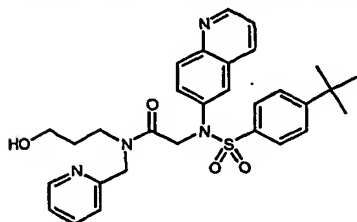


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
 LC-MS:  $rt = 0.75$  min, 533 (M+1, ES+).

5

**Example 117:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-(3-hydroxy-propyl)-N-pyridin-2-ylmethyl-acetamide:**



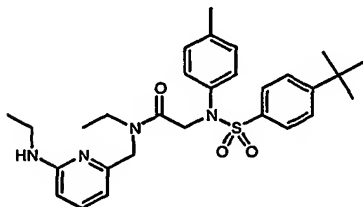
10

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with 3-[(pyridin-2-ylmethyl)-amino]-propan-1-ol  
 LC-MS:  $rt \approx 0.76$  min, 547 (M+1, ES+).

**Example 118:**

15

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(6-ethylamino-pyridin-2-ylmethyl)-acetamide:**

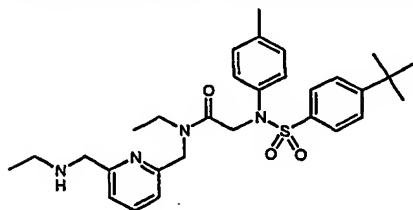


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(6-ethylaminomethyl-pyridin-2-yl)-amine  
 LC-MS:  $rt = 0.94$  min, 523 (M+1, ES+).

20

**Example 119:**

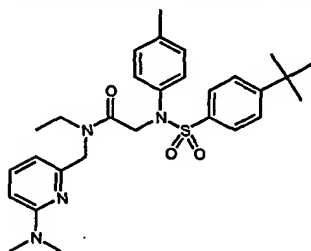
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-(6-ethylamino-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(6-ethylaminomethyl-pyridin-2-ylmethyl)-amine  
LC-MS: rt = 0.91 min, 537 (M+1, ES+).

**Example 120:**

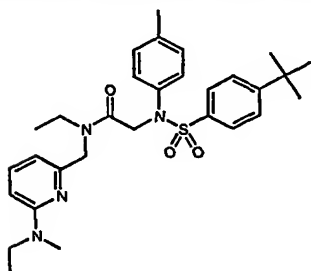
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-(6-dimethylamino-pyridin-2-ylmethyl)-N-ethyl-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with (6-ethylaminomethyl-pyridin-2-yl)-dimethyl-amine  
LC-MS: rt = 0.92 min, 523 (M+1, ES+).
- 15

**Example 121:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-ethyl-N-[6-(ethyl-methyl-amino)-pyridin-2-ylmethyl]-acetamide:**

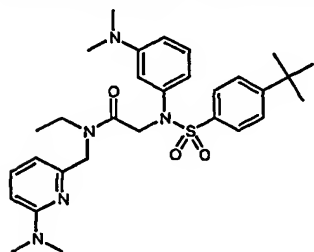


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid  
with ethyl-(6-ethylaminomethyl-pyridin-2-yl)-methyl-amine  
LC-MS: rt = 0.94 min, 537 (M+1, ES+).

5

**Example 122:**

**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-(6-dimethylamino-pyridin-2-ylmethyl)-N-ethyl-acetamide:**



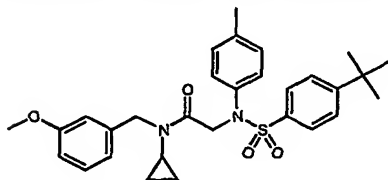
10

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-  
amino]-acetic acid with (6-ethylaminomethyl-pyridin-2-yl)-dimethyl-amine  
LC-MS: rt = 0.89 min, 552 (M+1, ES+).

**Example 123:**

15

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-cyclopropyl-N-(3-methoxy-benzyl)-acetamide:**

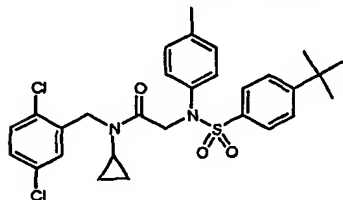


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid  
with cyclopropyl-(3-methoxy-benzyl)-amine  
LC-MS: rt = 1.14 min, 521 (M+1, ES+).

20

**Example 124:**

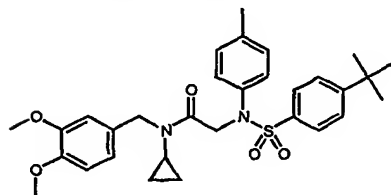
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-cyclopropyl-N-(2,5-dichloro-benzyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with cyclopropyl-(2,5-dichloro-benzyl)-amine  
LC-MS:  $rt = 1.16$  min, 559 (M+1, ES+).

**Example 125:**

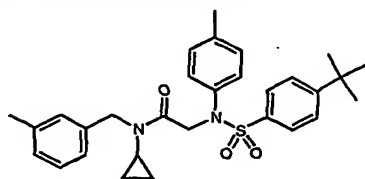
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-cyclopropyl-N-(3,4-dimethoxy-benzyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with cyclopropyl-(3,4-dimethoxy-benzyl)-amine  
15 LC-MS:  $rt = 1.12$  min, 551 (M+1, ES+).

**Example 126:**

**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-cyclopropyl-N-(3-methyl-benzyl)-acetamide:**

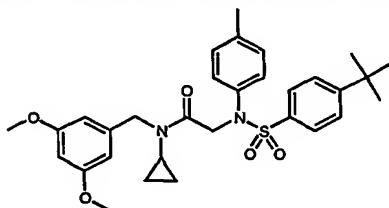


- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with cyclopropyl-(3-methyl-benzyl)-amine  
LC-MS:  $rt = 1.12$  min, 505 (M+1, ES+).



**Example 127:**

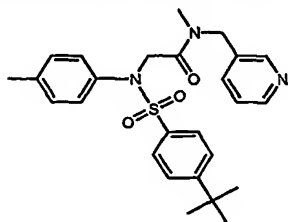
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-cyclopropyl-N-(3,5-dimethoxy-benzyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with cyclopropyl-(3,5-dimethoxy-benzyl)-amine  
LC-MS: rt = 1.15 min, 551 (M+1, ES+).

**Example 128:**

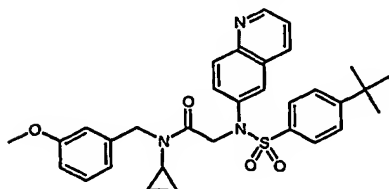
**2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N-methyl-N-pyridin-3-ylmethyl-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-p-tolyl-amino]-acetic acid with methyl-pyridin-3-ylmethyl-amine  
15 LC-MS: rt = 0.86 min, 466 (M+1, ES+).

**Example 129:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-N-cyclopropyl-N-(3-methoxy-benzyl)-acetamide:**

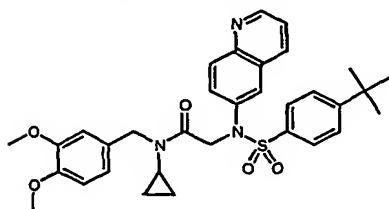


- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with cyclopropyl-(3-methoxy-benzyl)-amine

LC-MS: rt = 1.02 min, 558 (M+1, ES+).

**Example 130:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-cyclopropyl-*N*-(3,4-dimethoxy-benzyl)-acetamide:**

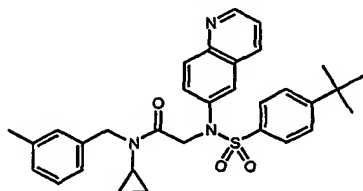


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with cyclopropyl-(3,4-dimethoxy-benzyl)-amine

LC-MS: rt = 0.99 min, 588 (M+1, ES+).

**Example 131:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-cyclopropyl-*N*-(3-methyl-benzyl)-acetamide:**

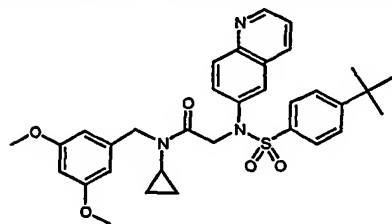


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with cyclopropyl-(3-methyl-benzyl)-amine

LC-MS: rt = 1.05 min, 542 (M+1, ES+).

**Example 132:**

**2-[(4-tert-Butyl-benzenesulfonyl)-quinolin-6-yl-amino]-*N*-cyclopropyl-*N*-(3,5-dimethoxy-benzyl)-acetamide:**

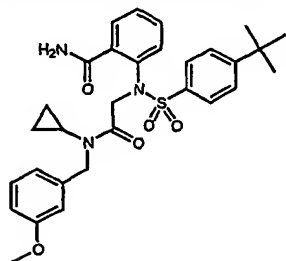


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-quinolin-6-yl-amino]-acetic acid with cyclopropyl-(3,5-dimethoxy-benzyl)-amine  
LC-MS: rt = 1.02 min, 588 (M+1, ES+).

5

**Example 133:**

**2-((4-tert-Butyl-benzenesulfonyl)-{[cyclopropyl-(3-methoxy-benzyl)-carbamoyl]-methyl}-amino)-benzamide:**



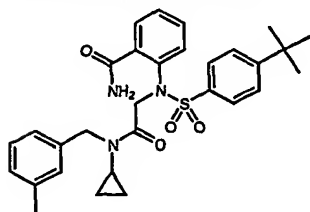
10

prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with cyclopropyl-(3-methoxy-benzyl)-amine  
LC-MS: rt = 1.05 min, 550 (M+1, ES+).

**Example 134:**

15

**2-((4-tert-Butyl-benzenesulfonyl)-{[cyclopropyl-(3-methyl-benzyl)-carbamoyl]-methyl}-amino)-benzamide:**

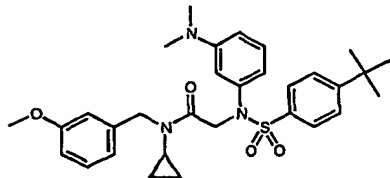


prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(2-carbamoyl-phenyl)-amino]-acetic acid with cyclopropyl-(3-methyl-benzyl)-amine  
LC-MS: rt = 1.07 min, 534 (M+1, ES+).

20

**Example 135:**

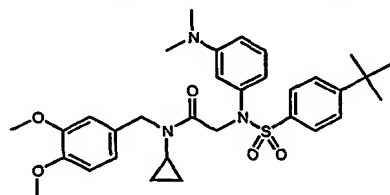
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-cyclopropyl-N-(3-methoxy-benzyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with cyclopropyl-(3-methoxy-benzyl)-amine  
LC-MS:  $t_r = 1.08$  min, 550 ( $M+1$ , ES+).

**Example 136:**

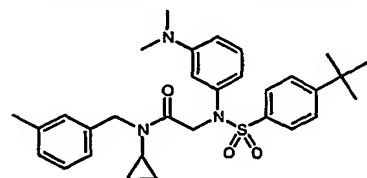
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-cyclopropyl-N-(3,4-dimethoxy-benzyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with cyclopropyl-(3,4-dimethoxy-benzyl)-amine  
15 LC-MS:  $t_r = 1.05$  min, 580 ( $M+1$ , ES+).

**Example 137:**

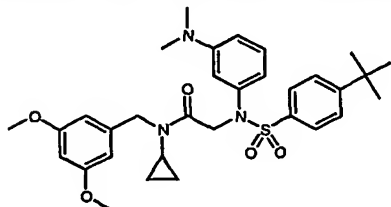
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-cyclopropyl-N-(3-methyl-benzyl)-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with cyclopropyl-(3-methyl-benzyl)-amine  
LC-MS:  $t_r = 1.10$  min, 534 ( $M+1$ , ES+).

**Example 138:**

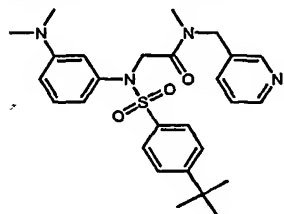
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-cyclopropyl-N-(3,5-dimethoxy-benzyl)-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with cyclopropyl-(3,5-dimethoxy-benzyl)-amine  
LC-MS:  $t_r = 1.08$  min, 580 (M+1, ES+).

**Example 139:**

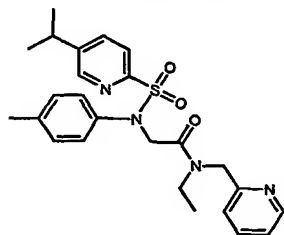
**2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-methyl-N-pyridin-3-ylmethyl-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-acetic acid with methyl-pyridin-3-ylmethyl-amine  
15 LC-MS:  $t_r = 0.81$  min, 495 (M+1, ES+).

**Example 140:**

**N-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-N-pyridin-2-ylmethyl-acetamide:**



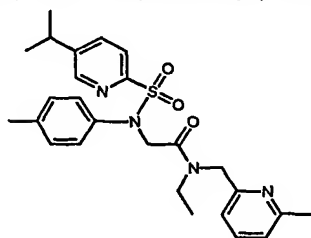
prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine

LC-MS:  $t_r = 0.84$  min, 467 (M+1, ES+).

5

#### Example 141:

***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



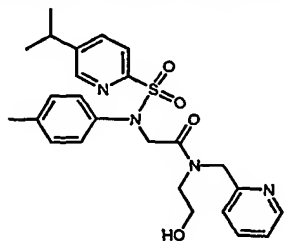
prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine

LC-MS:  $t_r = 0.83$  min, 481 (M+1, ES+).

10

#### Example 142:

***N*-(2-Hydroxy-ethyl)-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol

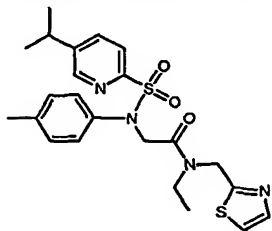
LC-MS:  $t_r = 0.79$  min, 483 (M+1, ES+).

15

20

**Example 143:**

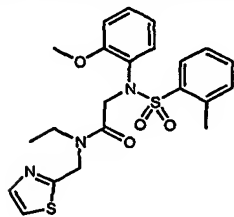
***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-*N*-thiazol-2-ylmethyl-acetamide:**



- 5 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-p-tolyl-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS: rt = 0.99 min, 473 (M+1, ES+).

**Example 144:**

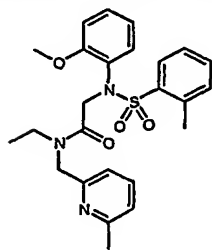
***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide:**



- 10 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
15 LC-MS: rt = 0.96 min, 460 (M+1, ES+).

**Example 145:**

***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



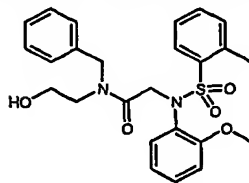
prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine

LC-MS:  $r_t = 0.80$  min, 468 (M+1, ES+).

5

#### Example 146:

*N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:



prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 2-benzylamino-ethanol

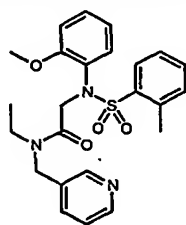
10

LC-MS:  $r_t = 0.96$  min, 469 (M+1, ES+).

#### Example 147:

*N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide:

15



prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine

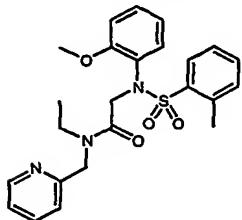
LC-MS:  $r_t = 0.78$  min, 454 (M+1, ES+).

20



**Example 148:**

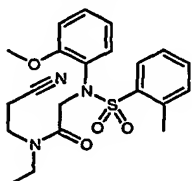
***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 5 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS:  $rt = 0.82$  min, 454 ( $M+1$ ,  $ES^+$ ).

**Example 149:**

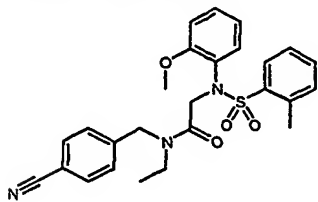
- 10 ***N*-(2-Cyano-ethyl)-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 15 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 3-ethylamino-propionitrile  
LC-MS:  $rt = 0.94$  min, 416 ( $M+1$ ,  $ES^+$ ).

**Example 150:**

***N*-(4-Cyano-benzyl)-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**

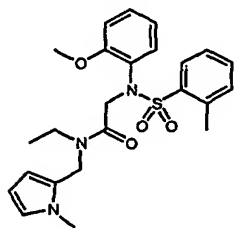


- 20 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 4-ethylaminomethyl-benzonitrile

LC-MS: rt = 1.03 min, 478 (M+1, ES+).

**Example 151:**

***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-(1-methyl-1H-pyrrol-2-ylmethyl)-acetamide:**

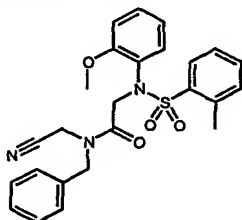


prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-(1-methyl-1H-pyrrol-2-ylmethyl)-amine

LC-MS: rt = 1.03 min, 456 (M+1, ES+).

**Example 152:**

***N*-Benzyl-*N*-cyanomethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**

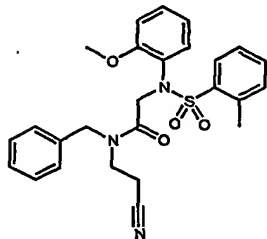


prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with benzylamino-acetonitrile

LC-MS: rt = 1.02 min, 464 (M+1, ES+).

**Example 153:**

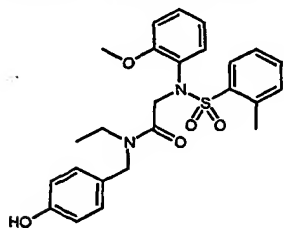
***N*-Benzyl-*N*-(2-cyano-ethyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 5 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 3-benzylamino-propionitrile  
LC-MS:  $rt = 1.02$  min, 478 ( $M+1$ ,  $ES^+$ ).

**Example 154:**

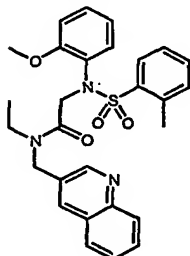
- 10 ***N*-Ethyl-*N*-(4-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 15 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 4-ethylaminomethyl-phenol  
LC-MS:  $rt = 0.85$  min, 469 ( $M+1$ ,  $ES^+$ ).

**Example 155:**

***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-quinolin-3-ylmethyl-acetamide:**



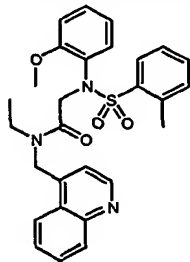
prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-quinolin-3-ylmethyl-amine

LC-MS: rt = 0.87 min, 504 (M+1, ES+).

5

### Example 156:

***N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-quinolin-4-ylmethyl-acetamide:**



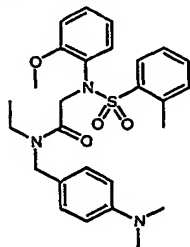
prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-quinolin-4-ylmethyl-amine

LC-MS: rt = 0.84 min, 504 (M+1, ES+).

10

### Example 157:

***N*-(4-Dimethylamino-benzyl)-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with (4-ethylaminomethyl-phenyl)-dimethyl-amine

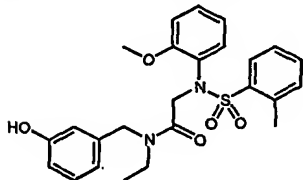
LC-MS: rt = 0.83 min, 496 (M+1, ES+).

15

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**Example 158:**

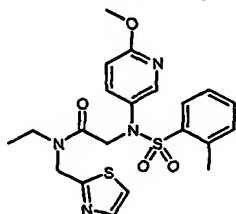
***N*-Ethyl-*N*-(3-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 5 prepared by reaction of [(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetic acid with 3-ethylaminomethyl-phenol  
LC-MS:  $t_r = 0.97$  min, 469 (M+1, ES+).

**Example 159:**

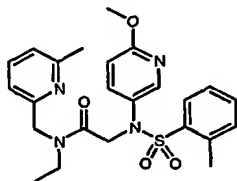
- 10 ***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide:**



- 15 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS:  $t_r = 0.93$  min, 461 (M+1, ES+).

**Example 160:**

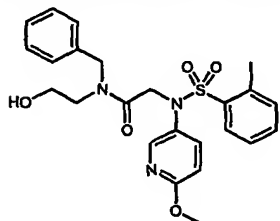
***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $t_r = 0.77$  min, 469 (M+1, ES+).

**Example 161:**

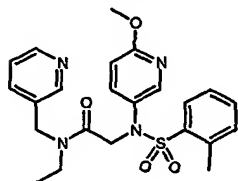
***N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 5 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with 2-benzylamino-ethanol  
LC-MS: *rt* = 0.93 min, 470 (*M*+1, ES+).

**Example 162:**

- 10 ***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide:**

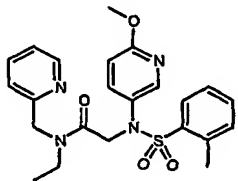


prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine

- 15 LC-MS: *rt* = 0.75 min, 455 (*M*+1, ES+).

**Example 163:**

***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



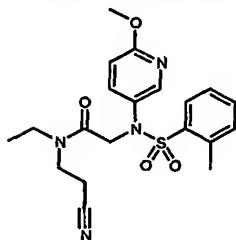
20

prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine

LC-MS: *rt* = 0.78 min, 455 (*M*+1, ES+).

**Example 164:**

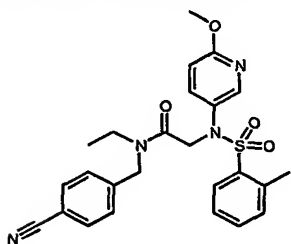
***N*-(2-Cyano-ethyl)-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 5 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with 3-ethylamino-propionitrile  
LC-MS: rt = 0.91 min, 417 (M+1, ES+).

**Example 165:**

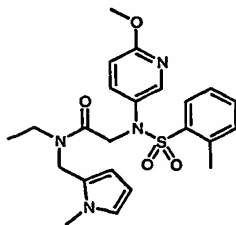
- 10 ***N*-(4-Cyano-benzyl)-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide:**



- 15 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with 4-ethylaminomethyl-benzonitrile  
LC-MS: rt = 1.00 min, 479 (M+1, ES+).

**Example 166:**

***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(1-methyl-1H-pyrrol-2-ylmethyl)-acetamide:**

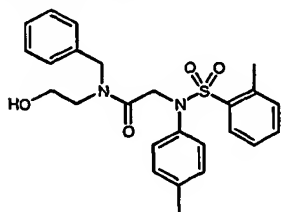


prepared by reaction of [(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetic acid with ethyl-(1-methyl-1H-pyrrol-2-ylmethyl)-amine  
LC-MS: rt = 1.00 min, 457 (M+1, ES+).

5

**Example 167:**

***N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**



prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with  
2-benzylamino-ethanol

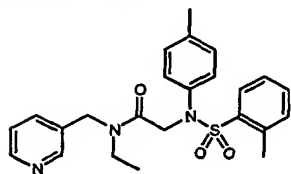
10

LC-MS: rt = 0.98 min, 453 (M+1, ES+).

**Example 168:**

***N*-Ethyl-*N*-pyridin-3-ylmethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

15



prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine

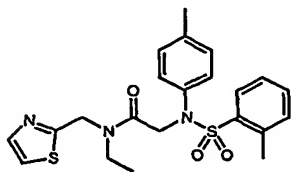
LC-MS: rt = 0.80 min, 438 (M+1, ES+).

20



**Example 169:**

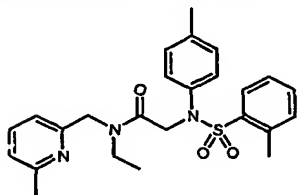
***N*-Ethyl-*N*-thiazol-2-ylmethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**



- 5 prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-thiazol-2-ylmethyl-amine  
LC-MS: *rt* = 0.98 min, 444 (*M*+1, ES+).

**Example 170:**

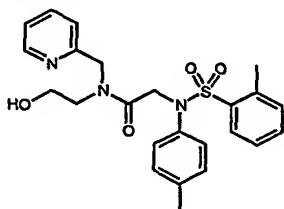
***N*-Ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**



- 10 prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
15 LC-MS: *rt* = 0.82 min, 452 (*M*+1, ES+).

**Example 171:**

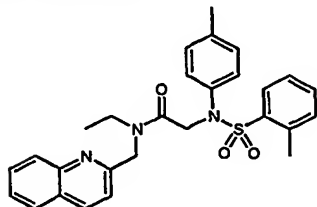
***N*-(2-Hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**



- 20 prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
LC-MS: *rt* = 0.78 min, 454 (*M*+1, ES+).

**Example 172:**

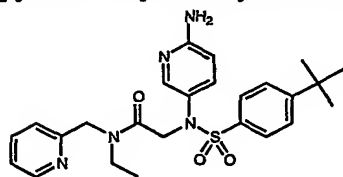
***N*-Ethyl-*N*-quinolin-2-ylmethyl-2-[(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**



- 5 prepared by reaction of [(toluene-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-quinolin-2-ylmethyl-amine  
LC-MS: *rt* = 0.94 min, 488 (*M*+1, ES+).

**Example 173:**

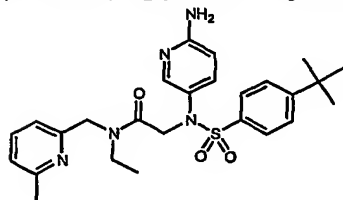
**2-[(6-Amino-pyridin-3-yl)-(4-*tert*-butyl-benzenesulfonyl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide:**



- 10 prepared by reaction of [(6-amino-pyridin-3-yl)-(4-*tert*-butyl-benzenesulfonyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
15 LC-MS: *rt* = 0.73 min, 482 (*M*+1, ES+).

**Example 174:**

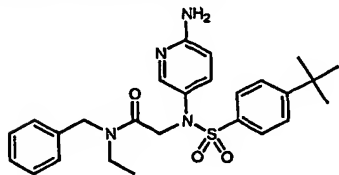
**2-[(6-Amino-pyridin-3-yl)-(4-*tert*-butyl-benzenesulfonyl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(6-amino-pyridin-3-yl)-(4-*tert*-butyl-benzenesulfonyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.71 min, 496 (*M*+1, ES+).

**Example 175:**

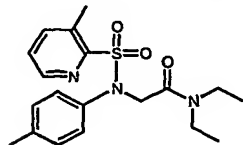
**2-[(6-Amino-pyridin-3-yl)-(4-tert-butyl-benzenesulfonyl)-amino]-*N*-benzyl-*N*-ethyl-acetamide:**



- 5 prepared by reaction of [(6-amino-pyridin-3-yl)-(4-tert-butyl-benzenesulfonyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS:  $t_r = 0.88$  min, 481 ( $M+1$ , ES+).

**Example 176:**

- 10 ***N,N*-Diethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetamide:**

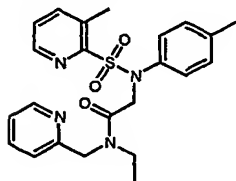


- prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with diethylamine  
LC-MS:  $t_r = 0.94$  min, 376 ( $M+1$ , ES+).

15

**Example 177:**

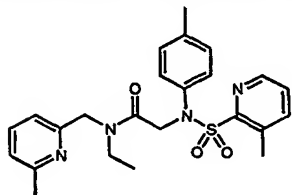
***N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS:  $t_r = 0.78$  min, 439 ( $M+1$ , ES+).

**Example 178:**

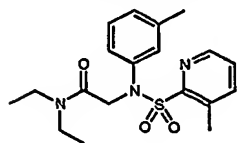
***N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.78 min, 453 (*M*+1, ES+).

**Example 179:**

- 10 ***N,N*-Diethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetamide:**

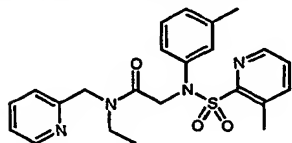


- prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid with diethylamine  
LC-MS: *rt* = 0.94 min, 376 (*M*+1, ES+).

15

**Example 180:**

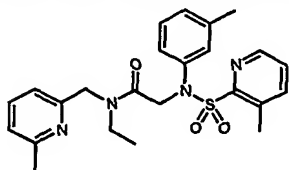
***N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS: *rt* = 0.78 min, 439 (*M*+1, ES+).

**Example 181:**

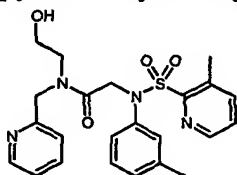
***N*-Ethyl-2-[(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $r_t = 0.78$  min, 453 ( $M+1$ , ES+).

**Example 182:**

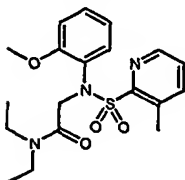
***N*-(2-Hydroxy-ethyl)-2-[(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 10 prepared by reaction of [(3-methyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
15 LC-MS:  $r_t = 0.72$  min, 455 ( $M+1$ , ES+).

**Example 183:**

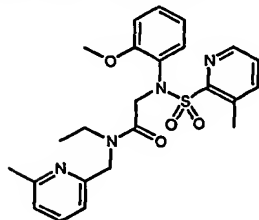
***N,N*-Diethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide:**



- 20 prepared by reaction of [(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with diethylamine  
LC-MS:  $r_t = 0.87$  min, 392 ( $M+1$ , ES+).

**Example 184:**

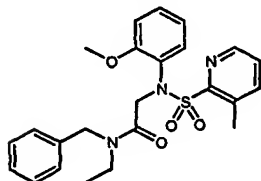
***N*-Ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.72 min, 469 (*M*+1, *ES*<sup>+</sup>).

**Example 185:**

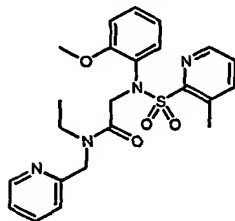
- 10 ***N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide:**



- 15 prepared by reaction of [(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS: *rt* = 0.98 min, 454 (*M*+1, *ES*<sup>+</sup>).

**Example 186:**

***N*-Ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**

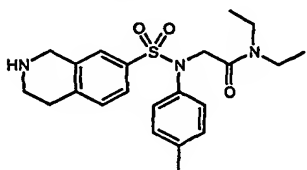


- 20 prepared by reaction of [(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine

LC-MS:  $rt = 0.70$  min, 455 ( $M+1$ ,  $ES^+$ ).

**Example 187:**

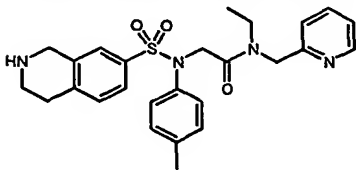
***N,N*-Diethyl-2-[(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetamide:**



prepared by reaction of [(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetic acid with diethylamine; due to the presence of formic acid in the eluent of the HPLC chromatography the product contained considerable amounts of *N,N*-diethyl-2-[(2-formyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetamide (LC-MS:  $rt = 0.91$  min, 444 ( $M+1$ ,  $ES^+$ ))  
LC-MS:  $rt = 0.74$  min, 416 ( $M+1$ ,  $ES^+$ ).

**Example 188:**

***N*-Ethyl-*N*-pyridin-2-ylmethyl-2-[(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetamide:**



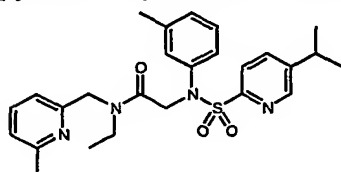
prepared by reaction of [(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine; due to the presence of formic acid in the eluent of the HPLC chromatography the product contained considerable amounts of *N*-ethyl-2-[(2-formyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-*p*-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide (LC-MS:  $rt = 0.77$  min, 507 ( $M+1$ ,  $ES^+$ ))  
LC-MS:  $rt = 0.64$  min, 479 ( $M+1$ ,  $ES^+$ ).

**E.4 Synthesis of sulfonylamino-acetic acids (EDC coupling):**

A solution of the respective acetic acid derivative (0.10 mmol) in DMF (1.0 mL) was treated with solutions of DMAP (0.30 mmol) and of EDC hydrochloride (0.15 mmol) in DMF. A solution of the respective amine (0.12 mmol) in DMF was added. The reaction mixture was stirred at RT for 12 h and purified by preparative HPLC chromatography to give the following sulfonamides:

**Example 189:**

***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**

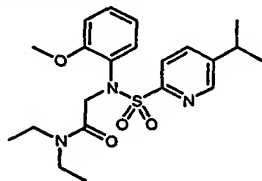


prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-*m*-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine

LC-MS: *rt* = 0.83 min, 481 (*M*+1, ES+).

**Example 190:**

***N,N*-Diethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetamide:**



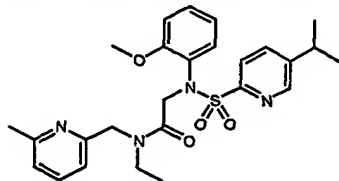
prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetic acid with diethylamine

LC-MS: *rt* = 0.96 min, 420 (*M*+1, ES+).



**Example 191:**

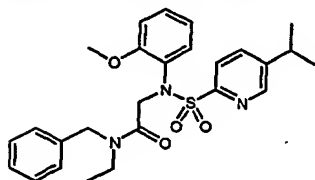
***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $t_r = 0.80$  min, 497 ( $M+1$ , ES $^+$ ).

**Example 192:**

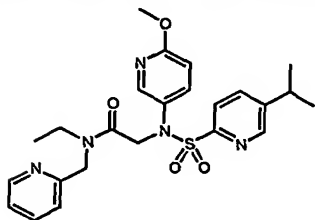
- 10 ***N*-Benzyl-*N*-ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetamide:**



- 15 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(2-methoxy-phenyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS:  $t_r = 1.05$  min, 482 ( $M+1$ , ES $^+$ ).

**Example 193:**

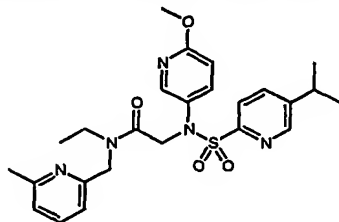
***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS:  $t_r = 0.80$  min, 484 ( $M+1$ , ES $^+$ ).

**Example 194:**

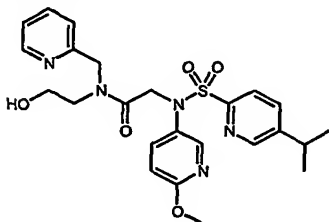
***N*-Ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS:  $rt = 0.79$  min, 498 ( $M+1$ ,  $ES^+$ ).

**Example 195:**

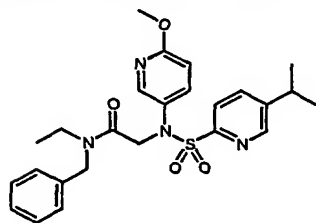
***N*-(2-Hydroxy-ethyl)-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 10 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
15 LC-MS:  $rt = 0.75$  min, 500 ( $M+1$ ,  $ES^+$ ).

**Example 196:**

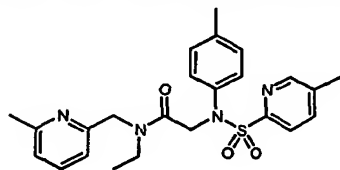
***N*-Benzyl-*N*-ethyl-2-[(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetamide:**



- 20 prepared by reaction of [(5-isopropyl-pyridine-2-sulfonyl)-(6-methoxy-pyridin-3-yl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS:  $rt = 1.03$  min, 483 ( $M+1$ ,  $ES^+$ ).

**Example 197:**

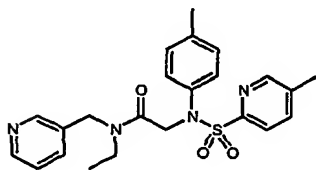
***N*-Ethyl-2-[(5-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 5 prepared by reaction of [(5-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.77 min, 453 (*M*+1, ES+).

**Example 198:**

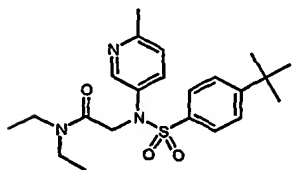
***N*-Ethyl-2-[(5-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-*N*-pyridin-3-ylmethyl-acetamide:**



- 10 prepared by reaction of [(5-methyl-pyridine-2-sulfonyl)-*p*-tolyl-amino]-acetic acid with ethyl-pyridin-3-ylmethyl-amine  
15 LC-MS: *rt* = 0.75 min, 439 (*M*+1, ES+).

**Example 199:**

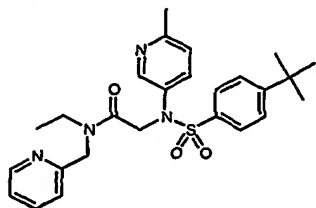
**2-[(4-*tert*-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N,N*-diethyl-acetamide:**



- 20 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid with diethylamine  
LC-MS: *rt* = 0.87 min, 418 (*M*+1, ES+).

**Example 200:**

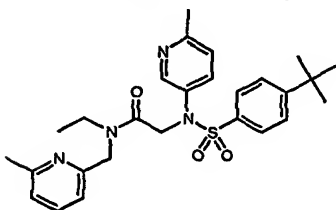
**2-[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide:**



- 5 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS:  $t_r = 0.78$  min, 481 ( $M+1$ , ES+).

**Example 201:**

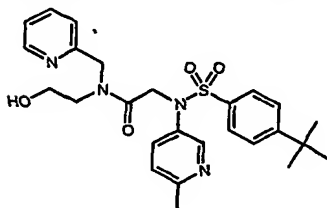
**2-[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 10 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
15 LC-MS:  $t_r = 0.77$  min, 495 ( $M+1$ , ES+).

**Example 202:**

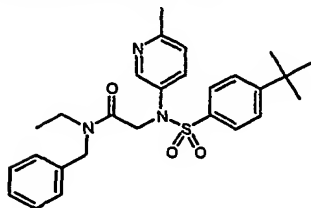
**2-[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide:**



- 20 prepared by reaction of [(4-tert-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
LC-MS:  $t_r = 0.72$  min, 497 ( $M+1$ , ES+).

**Example 203:**

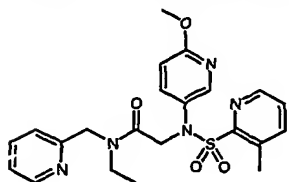
***N*-Benzyl-2-[(4-*tert*-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-acetamide:**



- 5 prepared by reaction of [(4-*tert*-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS: *rt* = 0.95 min, 480 (*M*+1, ES+).

**Example 204:**

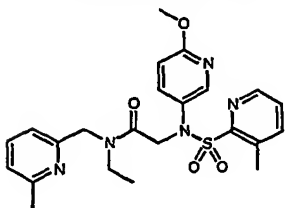
- 10 ***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 15 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with ethyl-pyridin-2-ylmethyl-amine  
LC-MS: *rt* = 0.70 min, 456 (*M*+1, ES+).

**Example 205:**

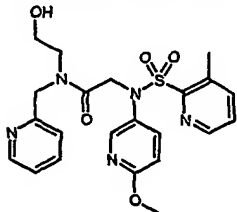
***N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide:**



- 20 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with ethyl-(6-methyl-pyridin-2-ylmethyl)-amine  
LC-MS: *rt* = 0.72 min, 470 (*M*+1, ES+).

**Example 206:**

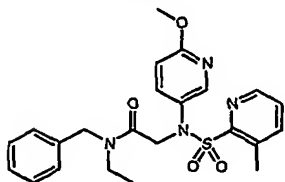
***N*-(2-Hydroxy-ethyl)-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide:**



- 5 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with 2-[(pyridin-2-ylmethyl)-amino]-ethanol  
LC-MS: rt = 0.67 min, 472 (M+1, ES+).

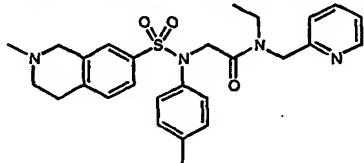
**Example 207:**

- 10 ***N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide:**



- 15 prepared by reaction of [(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetic acid with benzyl-ethyl-amine  
LC-MS: rt = 0.98 min, 455 (M+1, ES+).

- 20 **F Synthesis of *N*-Ethyl-2-[(2-methyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-p-tolyl-amino]-*N*-pyridin-2-ylmethyl-acetamide (Example 208):**



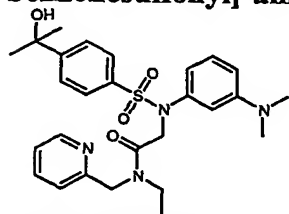
- 25 To a solution of *N*-ethyl-*N*-pyridin-2-ylmethyl-2-[(1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl)-p-tolyl-amino]-acetamide (0.46 mmol) in methanol (15 mL) was added a solution of formaldehyde in water (37%, 0.92 mL), sodium cyanoborohydride (675 mg) and acetic acid (3.07 mL). After 2 h a saturated NaHCO<sub>3</sub>-solution (25 mL), water (25 mL) and ethyl acetate (50 mL) were added, the layers were separated and

the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative HPLC chromatography to give 66.7 mg (0.14 mmol, 29%) of the desired product.

LC-MS:  $t_r$  = 0.65 min, 493 (M+1, ES+).

5

**G Synthesis of 2-[(3-Dimethylamino-phenyl)-[4-(1-hydroxy-1-methyl-ethyl)-benzenesulfonyl]-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide:**



10

(3-Dimethylamino-phenylamino)-acetic acid methyl ester:

To a solution of *N,N*-dimethyl-*m*-phenylenediamine (120 mmol) in THF (500 mL) was added methyl bromoacetate (132 mmol) and DIPEA (264 mmol). The reaction mixture was refluxed for 16 h. Water (200 mL) and ethyl acetate (300 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water (4 x 100 mL) and brine (100 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvents were removed in vacuo and the residue was purified by flash-chromatography (ethyl acetate/heptane 1:4) to give 17.5 g (84.0 mmol, 70%) of an oily product which crystallized slowly.

15

LC-MS:  $t_r$  = 0.51 min, 209 (M+1, ES+).

20

(3-Dimethylamino-phenylamino)-acetic acid:

To a solution of (3-dimethylamino-phenylamino)-acetic acid methyl ester (84 mmol) in methanol (300 mL) was added a solution of sodium hydroxide in water (2.0 mol/L, 150 mL) at 0°C. The reaction mixture was stirred at RT for 16 h and methanol was removed in vacuo. Water (200 mL) and ethyl acetate (300 mL) were added, the layers were separated and the aqueous layer was acidified to pH 2 by addition of hydrochloric acid (2.0 mol/L). The aqueous layer was extracted with ethyl acetate (3 x 200 mL) and concentrated in vacuo. Methanol (100 mL) was added and the obtained suspension was filtered. The filtrate was concentrated in vacuo and the obtained solid was crystallized from methanol / ethyl acetate to give 15.0 g (56.2

25

30

mmol, 67%) of (3-dimethylamino-phenylamino)-acetic acid dihydrochloride as pink crystals.

LC-MS:  $r_t = 0.40$  min, 195 (M+1, ES+).

5      2-(3-Dimethylamino-phenylamino)-N-ethyl-N-pyridin-2-ylmethyl-acetamide:

A suspension of ethyl-pyridin-2-ylmethyl-amine (41.1 mmol) and DIPEA (112 mmol) in DMF (200 mL) was cooled to  $-20^{\circ}\text{C}$  and added to a cold ( $-20^{\circ}\text{C}$ ) solution of (3-dimethylamino-phenylamino)-acetic acid (37.4 mmol) and TBTU (48.6 mmol) in DMF (300 mL). The reaction mixture was stirred for 10 min at  $-20^{\circ}\text{C}$ . Water (500 mL) and ethyl acetate (500 mL) were added, the layers were separated and the organic layer was washed with water (4 x 200 mL). The combined aqueous layers were extracted with ethyl acetate (300 mL). The combined organic layers were washed with NaOH solution (1.0 mol/L, 100 mL) and brine (100 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvents were removed in vacuo and the obtained solid was dissolved in ethanol. A solution of hydrogen chloride in ether was added at  $0^{\circ}\text{C}$ , the solvents were removed and the residue was crystallized from ethanol / ether to give 7.6 g product as white crystals.

LC-MS:  $r_t = 0.49$  min, 313 (M+1, ES+).

20      2-[(4-Acetyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide:

A solution of 2-(3-dimethylamino-phenylamino)-N-ethyl-N-pyridin-2-ylmethyl-acetamide (2.50 mmol) and of DIPEA (5.00 mmol) in THF (10 mL) was added to a solution of 4-acetyl-benzenesulfonyl chloride (2.50 mmol) in THF (10 mL). The reaction mixture was stirred for 2 h, the solvents were removed and the residue was purified by preparative HPLC chromatography to give 451 mg (0.91 mmol, 36%) product as a brownish foam.

LC-MS:  $r_t = 0.75$  min, 495 (M+1, ES+).

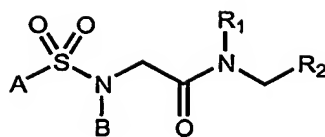


**Example 209****2-[(3-Dimethylamino-phenyl)-[4-(1-hydroxy-1-methyl-ethyl)-benzenesulfonyl]-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide:**

At -78°C a solution of methyllithium in ether (1.60 mol/L, 0.25 mL) was added to a solution of titanium(IV) chloride in DCM (1.00 mol/L, 0.40 mL). The reaction mixture was treated with a solution of 2-[(4-acetyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-N-ethyl-N-pyridin-2-ylmethyl-acetamide (0.10 mmol) in DCM (1.0 mL), allowed to reach RT, stirred for 1 h and purified by preparative HPLC chromatography.

LC-MS: rt = 0.70 min, 511 (M+1, ES+).

### 1. Compounds of formula (I)



### Formula (I)

A represents 4-ethylphenyl-, 4-isopropylphenyl-, 4-*tert*.-butylphenyl-, 2-methylphenyl-, 3-methylphenyl-, 4-cyclopropylphenyl-, 3-fluorophenyl-, 2-chlorophenyl-, 3-chlorophenyl-, 4-bromophenyl-, 2-trifluoromethylphenyl-, 3-trifluoromethylphenyl-, 4-(1-hydroxy-1-methyl-ethyl)-phenyl-, 3-chloro-4-methylphenyl-, 2-methoxy-4-methylphenyl-, 3,4-difluorophenyl-, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl, 2-formyl-1,2,3,4-tetrahydroisoquinolin-7-yl, phenylethenyl-, 1-naphthyl-, 2-naphthyl-, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 5-isopropyl-pyridin-2-yl, 6-dimethylamino-pyridin-3-yl, 6-bromo-5-chloro-pyridin-3-yl or 8-quinolinyl-;

B represents a phenyl, a 6-membered heteroaryl or a nine- or ten-membered bicyclic heteroaryl group, which groups are unsubstituted or independently mono- or di- substituted with cyano, halogen, hydroxy, lower alkyl, hydroxy lower alkyl, amino lower alkyl, aminocarbonyl lower alkyl, sulfonylamino lower alkyl, lower alkenyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl lower alkyloxy, amino, aminocarbonyl or sulfonylamino; or a cyclohexyl, 3-piperidinyl or 4-piperidinyl group, which groups are unsubstituted or mono-substituted with hydroxy, lower alkyl, hydroxy lower alkyl, aminocarbonyl lower alkyl, sulfonylamino lower alkyl, amino, aminocarbonyl or sulfonylamino;

with the proviso that in case A represents 2-methylphenyl- or 4-bromophenyl the phenyl ring as represented by B is substituted;

R<sup>1</sup> represents lower alkyl, cycloalkyl, hydroxy lower alkyl or cyano lower alkyl;

R<sup>2</sup> represents lower alkyl, lower alkenyl, hydroxy lower alkyl, amino lower alkyl, sulfonylamino lower alkyl, cycloalkyl; an unsubstituted or mono- or disubstituted phenyl group substituted independently with cyano, halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino; an unsubstituted

or mono- or di-substituted five- or six-membered heteroaryl group substituted independently with cyano, halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino; an unsubstituted or mono- or di-substituted nine- or ten-membered bicyclic heteroaryl group substituted independently with cyano,  
 5 halogen, hydroxy, lower alkyl, lower alkoxy, cycloalkyloxy, amino, amino lower alkyl, aminocarbonyl or sulfonylamino;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological  
 10 forms, thereof.

2. Compounds of formula (I) wherein:

A represents a 4-ethylphenyl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of  
 15 diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

3. Compounds of formula (I) wherein:

A represents a 4-isopropylphenyl group;

20 B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological  
 forms, thereof.

25 4. Compounds of formula (I) wherein:

A represents a 4-*tert*.-butylphenyl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and  
 30 the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

5. Compounds of formula (I) wherein:

A represents a 2-methylphenyl group;

B has the meaning given in claim 1 with the proviso that the phenyl group is substituted;

R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

6. Compounds of formula (I) wherein:

A represents a 3-methylphenyl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

7. Compounds of formula (I) wherein:

A represents a 4-(1-hydroxy-1-methyl-ethyl)-phenyl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

8. Compounds of formula (I) wherein:

A represents a 3-chloro-4-methylphenyl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

9. Compounds of formula (I) wherein:

A represents a 2-formyl-1,2,3,4-tetrahydroisoquinolin-7-yl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and

the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

10. Compounds of formula (I) wherein:

A represents a 2-naphthyl group;

5 B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

10 11. Compounds of formula (I) wherein:

A represents a 3-methyl-pyridin-2-yl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and  
15 the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

12. Compounds of formula (I) wherein:

A represents a 5-isopropyl-pyridin-2-yl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

20 and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological forms, thereof.

13. Compounds of formula (I) wherein:

25 A represents a 6-dimethylamino-pyridin-3-yl group;

B, R<sup>1</sup> and R<sup>2</sup> have the meaning given in claim 1;

and pure enantiomers, mixtures of enantiomers, pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates and the meso-form and pharmaceutically acceptable salts, solvent complexes, and morphological  
30 forms, thereof.

14. A compound according to claim 1, selected from the group consisting of

2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-N,N-diethyl-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(4-methoxy-phenyl)-amino]-N,N-diethyl-acetamide;

- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-methoxy-phenyl)-amino]-*N,N*-diethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*m*-tolyl-amino]-*N,N*-diethyl-acetamide;  
 2-[(6-Dimethylamino-pyridine-3-sulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-  
 acetamide;  
 5 *N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-4-ylmethyl-  
 acetamide;  
*N,N*-Diethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;  
*N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;  
 10 *N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;  
*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(2-methoxy-phenyl)-amino]-*N*-ethyl-  
 acetamide;  
*N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(naphthalene-2-sulfonyl)-amino]-  
 acetamide;  
 15 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-(2-hydroxy-ethyl)-acetamide;  
 2-[(3-Chloro-4-methyl-benzenesulfonyl)-*p*-tolyl-amino]-*N,N*-diethyl-acetamide;  
*N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-hydroxy-ethyl)-  
 acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-(2-cyano-ethyl)-*N*-ethyl-acetamide;  
 20 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-  
 acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-pyridin-3-ylmethyl-  
 acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-  
 25 ylmethyl)-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-*p*-tolyl-amino]-*N*-ethyl-*N*-thiazol-2-ylmethyl-  
 acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N,N*-diethyl-  
 acetamide;  
 30 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-pyridin-2-  
 ylmethyl-acetamide;  
 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-ethyl-*N*-(6-  
 methyl-pyridin-2-ylmethyl)-acetamide;

- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-ethyl-*N*-(3-hydroxy-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 5 2-[(4-tert-Butyl-benzenesulfonyl)-(1*H*-indazol-6-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-(2-hydroxy-ethyl)-*N*-pyridin-2-ylmethyl-acetamide;
- 10 2-[(4-tert-Butyl-benzenesulfonyl)-p-tolyl-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 2-[(4-tert-Butyl-benzenesulfonyl)-(3-dimethylamino-phenyl)-amino]-*N*-cyclopropyl-*N*-(3-methoxy-benzyl)-acetamide;
- 15 *N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-thiazol-2-ylmethyl-acetamide;
- N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;
- N*-Ethyl-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;
- 20 *N*-Ethyl-*N*-(3-hydroxy-benzyl)-2-[(2-methoxy-phenyl)-(toluene-2-sulfonyl)-amino]-acetamide;
- N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 25 *N*-Benzyl-*N*-(2-hydroxy-ethyl)-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-acetamide;
- N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-3-ylmethyl-acetamide;
- N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-*N*-pyridin-2-ylmethyl-acetamide;
- 30 *N*-Ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

*N*-Benzyl-*N*-ethyl-2-[(2-methoxy-phenyl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

2-[(4-tert-Butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-*N*-pyridin-2-ylmethyl-acetamide;

5 *N*-Benzyl-2-[(4-tert-butyl-benzenesulfonyl)-(6-methyl-pyridin-3-yl)-amino]-*N*-ethyl-acetamide;

*N*-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-*N*-(6-methyl-pyridin-2-ylmethyl)-acetamide;

10 *N*-Benzyl-*N*-ethyl-2-[(6-methoxy-pyridin-3-yl)-(3-methyl-pyridine-2-sulfonyl)-amino]-acetamide;

15. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, comprising one or more compounds of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.

16. Pharmaceutical compositions for the treatment of eating disorders, sleep disorders,  
15 cardiovascular disorders, cancer, pain, depression, anxiety, schizophrenia, neurodegenerative disorders or hyperthermia syndromes, comprising one or more compounds of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.

17. The compounds of any one of claims 1 to 14, or a pharmaceutically acceptable salt  
20 thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexins.

18. The compounds of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of eating disorders, sleep disorders, cardiovascular disorders, cancer, pain, depression, anxiety, schizophrenia,  
25 neurodegenerative disorders or hyperthermia syndromes.

19. A method of treating or preventing diseases or disorders where an antagonist of human orexin receptors is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.

30 20. A process for the manufacture of pharmaceutical compositions for the treatment of disorders mentioned in claim 15 or 16, containing one or more compounds as claimed in any one of claims 1 to 14, or a pharmaceutically acceptable salt or salts thereof, as active



ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.

21. Use of one or more compounds of any one of claims 1 to 14 in combination with other pharmacologically active compounds comprising other orexin receptor antagonists, lipid  
5 lowering agents, anorectic agents, sleep inducing agents, antidepressants or other drugs beneficial for the prevention or treatment of disorders given in any one of claims 15 to 19.

22. A compound as described as end-product in any one of examples 1 to 209.

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(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number  
**WO 2004/033418 A3**

(51) International Patent Classification<sup>7</sup>: **C07C 311/13**,  
311/20, 311/21, C07D 207/335, 209/14, 213/76, 213/75,  
215/36, 215/38, 217/02, 217/04, 217/12, 231/56, 233/61,  
277/28, A61K 31/18, 31/277, 31/40, 31/4045, 31/416,  
31/417, 31/426, 31/44, 31/47

(21) International Application Number:  
PCT/EP2003/011021

(22) International Filing Date: 6 October 2003 (06.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PCT/EP02/11409 11 October 2002 (11.10.2002) EP

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
3 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **SULFONYLAMINO-ACETIC DERIVATIVES AND THEIR USE AS OREXIN RECEPTOR ANTAGONISTS**

(57) Abstract: The invention relates to novel sulfonylamino-acetic acid derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of such compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

WO 2004/033418 A3

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EU 03/11021

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/13 C07C311/20 C07C311/21 C07D207/335 C07D209/14  
 C07D213/76 C07D213/75 C07D215/36 C07D215/38 C07D217/02  
 C07D217/04 C07D217/12 C07D231/56 C07D233/61 C07D277/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, EPO-Internal, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 68609 A (ACETELION PHARMACEUTICALS LTD) 20 September 2001 (2001-09-20) cited in the application claim 9	15-19
A	----- DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MALINOVSKII, M. S. ET AL: "Sulfanilides. I. N-Sulfonylarylglycine dialkylamides" retrieved from STN Database accession no. 1963:33088 XP002274762 abstract & ZHURNAL OBSHCHEI KHIMII (1962), 32, 726-8 , -----	1-14

☐ Further documents are listed in the continuation of box C.

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### \* Special categories of cited documents :

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\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the International filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the International search report

26/04/2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/11021

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/18 A61K31/277 A61K31/40 A61K31/4045 A61K31/416  
A61K31/417 A61K31/426 A61K31/44 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the international search report

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 03/11021

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 19 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP03/11021

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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